TITLE

Alpha-Ketoamide Inhibitors of Hepatitis C Virus NS3 Protease

FIELD OF THE INVENTION

The present invention relates generally to a novel class of alpha-ketoamides which are useful as serine protease inhibitors, and more particularly as Hepatitis C virus NS3 protease inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds and methods of using the same.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is the major cause of transfusion and community-acquired non-A, non-B hepatitis worldwide. Approximately 2% of the world's population are infected with the virus. In the Unites States, hepatitis C represents approximately 20% of cases of acute hepatitis. Unfortunately, self-limited hepatitis is not the most common course of acute HCV infection. In the majority of patients, symptoms of acute hepatitis resolve, but alanine aminotransferase (a liver enzyme diagnostic for liver damage) levels often remain elevated and HCV RNA persists. Indeed, a propensity to chroninicity is the most distinguishing characteristic of hepatitis C, occurring in at least 85% of patients with acute HCV infection. The factors that lead to chronicity in hepatitis C are not well defined. Chronic HCV infection is associated with increased incidence of liver cirrhosis and liver cancer. No vaccines are available for this virus, and current treatment is restricted to the use of alpha interferon, which is effective in only 15-20% of patients. Recent clinical studies have shown that combination therapy of alpha interferon and ribavirin leads to sustained efficacy in 40% of patients (Poynard, T. et al. *Lancet* **1998**, *352*, 1426-1432.). However, a majority of patients still either fail to respond or relapse after completion of therapy.

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Thus, there is a clear need to develop more effective therapeutics for treatment of HCV-associated hepatitis.

HCV is a positive-stranded RNA virus. Based on comparison of deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family, which also includes flaviviruses such as yellow fever virus and animal pestiviruses like bovine viral diarrhea virus and swine fever virus. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

The RNA genome is about 9.6 Kb in length, and encodes a single polypeptide of about 3000 amino acids. The 5' untranslated region contains an internal ribosome entry site (IRES), which directs cellular ribosomes to the correct AUG for initiation of translation. As was determined by transient expression of cloned HCV cDNAs, the precursor protein is cotranslationally and posttranslationally processed into at least 10 viral structural and nonstructural (NS) proteins by the action of a host signal peptidase and by two distinct viral proteinase activities. The translated product contains the following proteins: core-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B.

The N-terminal portion of NS3 functions as a proteolytic enzyme that is responsible for the cleavage of sites liberating the nonstructural proteins NS4A, NS4B,

NS5A, and NS5B. NS3 has further been shown to be a serine protease. Although the functions of the NS proteins are not completely defined, it is known that NS4A is a protease cofactor and NS5B is an RNA polymerase involved in viral replication. Thus agents that inhibit NS3 proteolytic processing of the viral polyprotein are expected to have antiviral activity.

There are several patents which disclose HCV NS3 protease inhibitors. WO98/17679 describes peptide and peptidomimetic ihibitors with the following formula: U-E^8-E^7-E^6-E^5-E^4-NH-CH(CH_2G^1)-W^1, where W is one of a variety of electrophilic groups, including boronic acid or ester. E4 represents either an amino acid or one of a series of peptidomimetic groups, the sythesis of which are not exemplified. HCV protease inhibitors described in the present case are not covered.

Based on the large number of persons currently infected with HCV and the limited treatments available, it is desirable to discover new inhibitors of HCV NS3 protease.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel HCV NS3 protease inhibitors.

It is another object of the present invention to provide a novel method of treating HCV infection which comprises administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

It is another object of the present invention to provide pharmaceutical compositions with HCV NS3 protease inhibiting activity comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

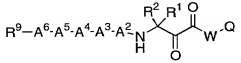
It is another object of the present invention to provide a method of inhibiting HCV present in a body fluid sample which comprises treating the body fluid sample with an effective amount of a compound of the present invention.

It is another object of the present invention to provide a kit or container containing at least one of the compounds of the present invention in an amount effective for use as a standard or reagent in a test or assay for determining the ability of a potential pharmaceutical to inhibit HCV NS3 protease, HCV growth, or both.

It is another object of the present invention to provide novel compounds for use in therapy.

It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of HCV.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of Formula (I):

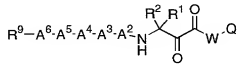


(I)

wherein W, Q, R^1, R^2, A^2, A^3, A^4, A^5, A^6, and R^9, are defined below, stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically acceptable salt forms thereof, are effective HCV NS3 protease inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides a novel compound of Formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

W is -NH- or -O-;

Q is selected from: $-(CR^{10}R^{10c})_n-Q^1$, $-(CR^{10}R^{10c})_n-Q^2$,
C_1-C_4 alkyl substituted with Q^1,
C_2-C_4 alkenyl substituted with Q^1,
C_2-C_4 alkynyl substituted with Q^1, and
an amino acid residue;

Q^1 is selected from:
$-CO_2R^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-P(O)_2R^{11}$, $-P(O)_3R^{11}$,
aryl substituted with 0-4 Q^{1a}, and
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Q^{1a};

Q^{1a} is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{19}$, $-C(=O)NR^{19}R^{19}$, $-NHC(=O)R^{19}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{19}$, $-NR^{19}R^{19}$, $-OR^{19}$, $-SR^{19}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{19} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, aryl(C_1-C_4 alkyl), C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl);

alternatively, $NR^{19}R^{19}$ may form a 5-6 membered heterocyclic group consisting of carbon atoms, a nitrogen atom, and optionally a second heteroatom selected from the group: O, S, and N;

R^{10} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, and C_1-C_6 alkyl substituted with 0-1 R^{10a};

R^{10a} is selected from the group: halo, $-NO_2$, $-CN$, $-CF_3$, $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with 0-1 R^{10b};

R^{10b} is selected from the group: $-CO_2H$, $-NH_2$, $-OH$, $-SH$, and $-C(=NH)NH_2$;

R^{10c} is H or C_1-C_4 alkyl;

alternatively, R^{10} and R^{10c} can be combined to form a C_3-C_6 cycloalkyl group substituted with 0-1 R^{10a};

R^{11} is, at each occurrence, independently H or C_1-C_4 alkyl;

R^{11a} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

Q^2 is $-X-NR^{12}-Z$, $-NR^{12}-Y-Z$, or $-X-NR^{12}-Y-Z$;

X is selected from the group: $-C(=O)-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-P(O)-$, $-P(O)_2-$, and $-P(O)_3-$;

Y is selected from the group: $-C(=O)-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-P(O)-$, $-P(O)_2-$, and $-P(O)_3-$;

R^{12} is H or C_1-C_4 alkyl;

Z is C_1-C_4 haloalkyl,
C_1-C_4 alkyl substituted with 0-3 Z^a,
C_2-C_4 alkenyl substituted with 0-3 Z^a,
C_2-C_4 alkynyl substituted with 0-3 Z^a,
C_3-C_{10} cycloalkyl substituted with 0-5 Z^b,
C_3-C_{10} carbocyle substituted with 0-5 Z^b,

aryl substituted with 0-5 Z^b,

5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Z^b;

an amino acid residue, or

$-A^7-A^8-A^9$;

Z^a is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy,

C_3-C_{10} cycloalkyl substituted with 0-5 Z^b,

C_3-C_{10} carbocyle substituted with 0-5 Z^b,

aryl substituted with 0-5 Z^b, or

5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Z^b;

Z^b is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy,

C_3-C_{10} cycloalkyl substituted with 0-5 Z^c,

C_3-C_{10} carbocyle substituted with 0-5 Z^c,

aryl substituted with 0-5 Z^c, or

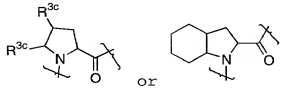
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Z^c;

Z^c is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{20} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

alternatively, $NR^{20}R^{20}$ may form a 5-6 membered heterocyclic group consisting of carbon atoms, a nitrogen atom, and optionally a second heteroatom selected from the group: O, S, and N;

A^2 is a bond, $-NH-CR^3R^4-C(=O)-$, an amino acid residue,



;

A^3 is a bond, $-NH-CR^5R^6-C(=O)-$, or an amino acid residue;

A^4 is a bond, $-NH-CR^7R^8-C(=O)-$, or an amino acid residue;

A^5 is a bond or an amino acid residue;

A^6 is a bond or an amino acid residue;

A^7 is a bond or an amino acid residue;

A^8 is an amino acid residue;

A^9 is an amino acid residue;

R^1 is selected from the group: H, F,
C_1-C_6 alkyl substituted with 0-3 R^{1a},
C_2-C_6 alkenyl substituted with 0-3 R^{1a},
C_2-C_6 alkynyl substituted with 0-3 R^{1a},
aryl substituted with 0-5 R^{1a}, and
C_3-C_6 cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:
Cl, F, Br, I, CF_3, CHF_2, OH, =O, SH, $-CO_2R^{1b}$, $-SO_2R^{1b}$,
$-SO_3R^{1b}$, $-P(O)_2R^{1b}$, $-P(O)_3R^{1b}$, $-C(=O)NHR^{1b}$, $-NHC(=O)R^{1b}$,
$-SO_2NHR^{1b}$, $-OR^{1b}$, $-SR^{1b}$, C_1-C_3 alkyl, C_3-C_6 cycloalkyl,
C_1-C_6 alkoxy, -S-(C_1-C_6 alkyl),
aryl substituted with 0-5 R^{1c},
$-O-(CH_2)_q$-aryl substituted with 0-5 R^{1c},
$-S-(CH_2)_q$-aryl substituted with 0-5 R^{1c}, and
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and substituted with 0-3 R^{1c};

R^{1b} is H,
C_1-C_4 alkyl substituted with 0-3 R^{1c},
C_2-C_4 alkenyl substituted with 0-3 R^{1c},
C_2-C_4 alkynyl substituted with 0-3 R^{1c},
C_3-C_6 cycloalkyl substituted with 0-5 R^{1c},
C_3-C_6 carbocyle substituted with 0-5 R^{1c},
aryl substituted with 0-5 R^{1c}, or
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 R^{1c};

R^{1c} is selected at each occurrence from: C_1-C_4 alkyl, Cl,
F, Br, I, OH, C_1-C_4 alkoxy, -CN, $-NO_2$, $C(O)OR^{1d}$,
$NR^{1d}R^{1d}$, CF_3, and OCF_3;

R^{1d} is H or C_1-C_4 alkyl;

R^2 is H, F, or C_1-C_4 alkyl;

R^3 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-4 R^{3a},
C_2-C_6 alkenyl substituted with 0-4 R^{3a},
C_2-C_6 alkynyl substituted with 0-4 R^{3a},
$-(CH_2)_q$- C_3-C_6 cycloalkyl substituted with 0-4 R^{3b},
$-(CH_2)_q$-aryl substituted with 0-5 R^{3b}, or
$-(CH_2)_q$-5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-2 R^{3b};

R^{3a} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with R^{10b};

R^{3b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{3c} is, at each occurrence, independently selected from: H, C_1-C_6 alkyl, -OH, and OR^{3d};

R^{3d} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_q$- C_3-C_6 cycloalkyl, $-(CH_2)_q$-aryl, or $-(CH_2)_q$-(5-10 membered heterocyclic group), wherein said heterocyclic group consists of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N;

R^4 is selected from the group: H, C_1-C_6 alkyl, phenyl, phenylmethyl-, phenylethyl-, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl-, and C_3-C_6 cycloalkylethyl-;

R^5 and R^7 are independently H or R^3;

R^6 and R^8 are independently H or R^4;

R^9 is selected from the group: $-S(=O)R^{9a}$, $-S(=O)_2R^{9a}$, $-C(=O)R^{9a}$, $-C(=O)OR^{9a}$, $-C(=O)NHR^{9a}$, C_1-C_3 alkyl-R^{9a}, C_2-C_6 alkenyl-R^{9a}, and C_2-C_6 alkynyl-R^{9a};

R^{9a} is selected from the group:
- C_1-C_6 alkyl substituted with 0-3 R^{9b},
- C_3-C_6 cycloalkyl substituted with 0-3 R^{9c},
- aryl substituted with 0-3 R^{9c}, and
- 5-14 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-3 R^{9c};

R^{9b} is selected from the group: phenyl, naphthyl, benzyl, and 5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and R^{9b} is substituted with 0-3 R^{9c};

R^{9c} is selected at each occurrence from the group:
- CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, NO_2;
- C_1-C_4 alkyl substituted with 0-3 R^{9d},
- C_1-C_4 alkoxy substituted with 0-3 R^{9d},
- C_3-C_6 cycloalkyl substituted with 0-3 R^{9d},
- aryl substituted with 0-5 R^{9d}, and
- 5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-4 R^{9d};

R^{9d} is selected at each occurrence from the group: C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, and NO_2;

an amino acid residue, at each occurence, independently comprises a natural amino acid, a modified amino acid or an unnatural amino acid wherein said natural, modified or unnatural amino acid is of either D or L configuration;

n is 1, 2, 3, or 4; and

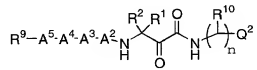
p is 1 or 2; and

q, at each occurence, is independently 0, 1 or 2.

[2] In a preferred embodiment, the present invention provides novel compounds of Formula I, wherein:

Q is $-(CR^{10}R^{10c})_n-Q^2$ or an amino acid residue, wherein the amino acid residue comprises a natural, a modified or an unnatural amino acid.

[3] In a more preferred embodiment, the present invention provides novel compounds of Formula II, wherein:



(II)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

R^{10} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, and C_1-C_6 alkyl substituted with 0-1 R^{10a};

R^{10a} is selected from the group: halo, $-NO_2$, -CN, $-CF_3$, $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with 0-1 R^{10b};

R^{10b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{10c} is H or C_1-C_4 alkyl;

alternatively, R^{10} and R^{10c} can be combined to form a C_3-C_6 cycloalkyl group substituted with 0-1 R^{10a};

R^{11} is, at each occurrence, independently H or C_1-C_4 alkyl;

R^{11a} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

Q^2 is $-X-NR^{12}-Z$, $-NR^{12}-Y-Z$, or $-X-NR^{12}-Y-Z$;

X is selected from the group: -C(=O)-, -S-, -S(=O)-, $-S(=O)_2-$, -P(O)-, $-P(O)_2-$, and $-P(O)_3-$;

Y is selected from the group: -C(=O)-, -S-, -S(=O)-, $-S(=O)_2-$, -P(O)-, $-P(O)_2-$, and $-P(O)_3-$;

R^{12} is H or C_1-C_4 alkyl;

Z is C_1-C_4 haloalkyl,
C_1-C_4 alkyl substituted with 0-3 Z^a,
C_2-C_4 alkenyl substituted with 0-3 Z^a,
C_2-C_4 alkynyl substituted with 0-3 Z^a,

C_3-C_{10} cycloalkyl substituted with 0-5 Z^b,
C_3-C_{10} carbocyle substituted with 0-5 Z^b,
aryl substituted with 0-5 Z^b,
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Z^b;
an amino acid residue, or
$-A^7-A^8-A^9$;

Z^a is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy,

C_3-C_{10} cycloalkyl substituted with 0-5 Z^b,
C_3-C_{10} carbocyle substituted with 0-5 Z^b,
aryl substituted with 0-5 Z^b, or
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Z^b;

Z^b is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy,

C_3-C_{10} cycloalkyl substituted with 0-5 Z^c,
C_3-C_{10} carbocyle substituted with 0-5 Z^c,
aryl substituted with 0-5 Z^c, or
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group:

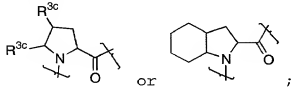
O, S, and N, said heterocyclic group substituted with 0-4 Z^c;

Z^c is H, F, Cl, Br, I, $-NO_2$, $-CN$, $-NCS$, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{20} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

alternatively, $NR^{20}R^{20}$ may form a 5-6 membered heterocyclic group consisting of carbon atoms, a nitrogen atom, and optionally a second heteroatom selected from the group: O, S, and N;

A^2 is a bond, $-NH-CR^3R^4-C(=O)-$, an amino acid residue,



;

A^3 is a bond, $-NH-CR^5R^6-C(=O)-$, or an amino acid residue;

A^4 is a bond, $-NH-CR^7R^8-C(=O)-$, or an amino acid residue;

A^5 is a bond or an amino acid residue;

A^7 is a bond or an amino acid residue;

A^8 is an amino acid residue;

A^9 is an amino acid residue;

R^1 is selected from the group: H, F,
C_1-C_6 alkyl substituted with 0-3 R^{1a},
C_2-C_6 alkenyl substituted with 0-3 R^{1a},
C_2-C_6 alkynyl substituted with 0-3 R^{1a}, and
C_3-C_6 cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:
Cl, F, Br, I, CF_3, CHF_2, OH, =O, SH, $-CO_2R^{1b}$, $-SO_2R^{1b}$,
$-SO_3R^{1b}$, $-P(O)_2R^{1b}$, $-P(O)_3R^{1b}$, $-C(=O)NHR^{1b}$, $-NHC(=O)R^{1b}$,
$-SO_2NHR^{1b}$, $-OR^{1b}$, $-SR^{1b}$, C_1-C_3 alkyl, C_3-C_6 cycloalkyl,
C_1-C_6 alkoxy, -S-(C_1-C_6 alkyl),
aryl substituted with 0-5 R^{1c},
$-O-(CH_2)_q$-aryl substituted with 0-5 R^{1c},
$-S-(CH_2)_q$-aryl substituted with 0-5 R^{1c}, and
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and substituted with 0-3 R^{1c};

R^{1b} is H,
C_1-C_4 alkyl substituted with 0-3 R^{1c},
C_2-C_4 alkenyl substituted with 0-3 R^{1c},
C_2-C_4 alkynyl substituted with 0-3 R^{1c},
C_3-C_6 cycloalkyl substituted with 0-5 R^{1c},
C_3-C_6 carbocyle substituted with 0-5 R^{1c},
aryl substituted with 0-5 R^{1c}, or
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 R^{1c};

R^{1c} is selected at each occurrence from: C_1-C_4 alkyl, Cl, F, Br, I, OH, C_1-C_4 alkoxy, -CN, $-NO_2$, $C(O)OR^{1d}$, $NR^{1d}R^{1d}$, CF_3, and OCF_3;

R^{1d} is H or C_1-C_4 alkyl;

R^2 is H, F, or C_1-C_4 alkyl;

R^3 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-4 R^{3a},
C_2-C_6 alkenyl substituted with 0-4 R^{3a},
C_2-C_6 alkynyl substituted with 0-4 R^{3a},
$-(CH_2)_q$- C_3-C_6 cycloalkyl substituted with 0-4 R^{3b},
$-(CH_2)_q$-aryl substituted with 0-5 R^{3b}, and
$-(CH_2)_q$-5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-2 R^{3b};

R^{3a} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with R^{10b};

R^{3b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{3c} is, at each occurrence, independently selected from: H, C_1-C_6 alkyl, -OH, and OR^{3d};

R^{3d} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_q$- C_3-C_6 cycloalkyl, $-(CH_2)_q$-aryl, or $-(CH_2)_q$-(5-10 membered heterocyclic group), wherein said heterocyclic group consists of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N;

R^4 is selected from the group: H, C_1-C_6 alkyl, phenyl, phenylmethyl-, phenylethyl-, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl-, and C_3-C_6 cycloalkylethyl-;

R^5 and R^7 are independently H or R^3;

R^6 and R^8 are independently H or R^4;

R^9 is selected from the group: $-S(=O)R^{9a}$, $-S(=O)_2R^{9a}$, $-C(=O)R^{9a}$, $-C(=O)OR^{9a}$, $-C(=O)NHR^{9a}$, C_1-C_3 alkyl-R^{9a}, C_2-C_6 alkenyl-R^{9a}, and C_2-C_6 alkynyl-R^{9a};

R^{9a} is selected from the group:
C_1-C_6 alkyl substituted with 0-3 R^{9b},
C_3-C_6 cycloalkyl substituted with 0-3 R^{9c},
aryl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-3 R^{9c};

R^{9b} is selected from the group: phenyl, naphthyl, benzyl, and 5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and R^{9b} is substituted with 0-3 R^{9c};

R^{9c} is selected at each occurrence from the group:
CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, NO_2;
C_1-C_4 alkyl substituted with 0-3 R^{9d},
C_1-C_4 alkoxy substituted with 0-3 R^{9d},
C_3-C_6 cycloalkyl substituted with 0-3 R^{9d},
aryl substituted with 0-5 R^{9d}, and
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-4 R^{9d};

R^{9d} is selected at each occurrence from the group: C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, and NO_2;

n is 1, 2, or 3; and

p is 1 or 2; and

q, at each occurence, is independently 0, 1 or 2.

[4] In a further more preferred embodiment, the present invention provides novel compounds of Formula II, wherein:

R^{10} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, and C_1-C_6 alkyl substituted with 0-1 R^{10a};

R^{10a} is selected from the group: halo, $-NO_2$, -CN, $-CF_3$, $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with 0-1 R^{10b};

R^{10b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{10c} is H or C_1-C_4 alkyl;

alternatively, R^{10} and R^{10c} can be combined to form a C_3-C_6 cycloalkyl group substituted with 0-1 R^{10a};

R^{11} is, at each occurrence, independently H or C_1-C_4 alkyl;

R^{11a} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

Q^2 is -X-NR^{12}-Z, -NR^{12}-Y-Z, or -X-NR^{12}-Y-Z;

X is selected from the group: -C(=O)-, -S-, -S(=O)-, and -$S(=O)_2$-;

Y is selected from the group: -C(=O)-, -S-, -S(=O)-, and -$S(=O)_2$-;

R^{12} is H or C_1-C_4 alkyl;

Z is C_1-C_4 haloalkyl,
C_1-C_4 alkyl substituted with 0-3 Z^a,
C_2-C_4 alkenyl substituted with 0-3 Z^a,
C_2-C_4 alkynyl substituted with 0-3 Z^a,
C_3-C_{10} cycloalkyl substituted with 0-5 Z^b,
C_3-C_{10} carbocyle substituted with 0-5 Z^b,
aryl substituted with 0-5 Z^b,
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Z^b;
an amino acid residue, or
-A^7-A^8-A^9;

Z^a is H, F, Cl, Br, I, -NO_2, -CN, -NCS, -CF_3, -OCF_3, -CH_3, -OCH_3, -CO_2R^{20}, -C(=O)$NR^{20}R^{20}$, -NHC(=O)R^{20}, -$NR^{20}R^{20}$, -OR^{20}, -SR^{20}, -S(=O)R^{20}, -SO_2R^{20}, -$SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy,

C_3-C_{10} cycloalkyl substituted with 0-5 Z^b,
C_3-C_{10} carbocyle substituted with 0-5 Z^b,
aryl substituted with 0-5 Z^b, or
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group:

O, S, and N, said heterocyclic group substituted with 0-4 Z^b;

Z^b is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy,

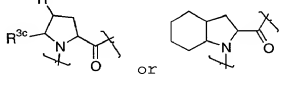
C_3-C_{10} cycloalkyl substituted with 0-5 Z^c,
C_3-C_{10} carbocyle substituted with 0-5 Z^c,
aryl substituted with 0-5 Z^c, or
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Z^c;

Z^c is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{20} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

alternatively, $NR^{20}R^{20}$ may form a piperidinyl, piperazinyl, or morpholinyl group;

A^2 is a bond, $-NH-CR^3R^4-C(=O)-$, an amino acid residue,



;

A^3 is a bond or an amino acid residue;

A^4 is a bond or an amino acid residue;

A^5 is a bond;

R^1 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-3 R^{1a},
C_2-C_6 alkenyl substituted with 0-3 R^{1a},
C_2-C_6 alkynyl substituted with 0-3 R^{1a}, and
C_3-C_6 cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:
Cl, F, Br, I, CF_3, CHF_2, OH, =O, SH, $-CO_2R^{1b}$, $-SO_2R^{1b}$,
$-SO_3R^{1b}$, $-P(O)_2R^{1b}$, $-P(O)_3R^{1b}$, $-C(=O)NHR^{1b}$, $-NHC(=O)R^{1b}$,
$-SO_2NHR^{1b}$, $-OR^{1b}$, $-SR^{1b}$, C_1-C_3 alkyl, C_3-C_6 cycloalkyl,
C_1-C_6 alkoxy, -S-(C_1-C_6 alkyl),
aryl substituted with 0-5 R^{1c},
$-O-(CH_2)_q$-aryl substituted with 0-5 R^{1c},
$-S-(CH_2)_q$-aryl substituted with 0-5 R^{1c}, and
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and substituted with 0-3 R^{1c};

R^{1b} is H,
C_1-C_4 alkyl substituted with 0-3 R^{1c},
C_2-C_4 alkenyl substituted with 0-3 R^{1c},
C_2-C_4 alkynyl substituted with 0-3 R^{1c},
C_3-C_6 cycloalkyl substituted with 0-5 R^{1c},
C_3-C_6 carbocyle substituted with 0-5 R^{1c},
aryl substituted with 0-5 R^{1c}, or
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group:

O, S, and N, said heterocyclic group substituted with 0-4 R^{1c};

R^{1c} is selected at each occurrence from: C_1-C_4 alkyl, Cl, F, Br, I, OH, C_1-C_4 alkoxy, -CN, $-NO_2$, $C(O)OR^{1d}$, $NR^{1d}R^{1d}$, CF_3, and OCF_3;

R^{1d} is H or C_1-C_4 alkyl;

R^2 is H or C_1-C_4 alkyl;

R^3 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-4 R^{3a},
C_2-C_6 alkenyl substituted with 0-4 R^{3a},
C_2-C_6 alkynyl substituted with 0-4 R^{3a},
$-(CH_2)_q$- C_3-C_6 cycloalkyl substituted with 0-4 R^{3b},
$-(CH_2)_q$-aryl substituted with 0-5 R^{3b}, and
$-(CH_2)_q$-5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-2 R^{3b};

R^{3a} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with R^{10b};

R^{3b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{3c} is, at each occurrence, independently selected from: H, C_1-C_6 alkyl, -OH, and OR^{3d};

R^{3d} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_q$-C_3-C_6 cycloalkyl, $-(CH_2)_q$-aryl, or $-(CH_2)_q$-(5-10 membered heterocyclic group), wherein said heterocyclic group consists of carbon atoms

and 1-4 heteroatoms selected from the group: O, S, and N;

R^4 is selected from the group: H, C_1-C_6 alkyl, phenyl, phenylmethyl-, phenylethyl-, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl-, and C_3-C_6 cycloalkylethyl-;

R^9 is selected from the group: $-S(=O)_2R^{9a}$, $-C(=O)R^{9a}$, C_1-C_3 alkyl-R^{9a}, C_2-C_6 alkenyl-R^{9a}, and C_2-C_6 alkynyl-R^{9a};

R^{9a} is selected from the group:
C_1-C_6 alkyl substituted with 0-3 R^{9b},
C_3-C_6 cycloalkyl substituted with 0-3 R^{9c},
aryl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-3 R^{9c};

R^{9b} is selected from the group: phenyl, naphthyl, benzyl, and 5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and R^{9b} is substituted with 0-3 R^{9c};

R^{9c} is selected at each occurrence from the group:
CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, NO_2;
C_1-C_4 alkyl substituted with 0-3 R^{9d},
C_1-C_4 alkoxy substituted with 0-3 R^{9d},
C_3-C_6 cycloalkyl substituted with 0-3 R^{9d},
aryl substituted with 0-5 R^{9d}, and
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the

group: O, S, and N, and said heterocyclic group is substituted with 0-4 R^{9d};

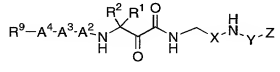
R^{9d} is selected at each occurrence from the group: C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, and NO_2;

n is 1 or 2; and

p is 1 or 2; and

q, at each occurence, is independently 0, 1 or 2.

[5] In an even more preferred embodiment, the present invention provides novel compounds of Formula III, wherein:



(III)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

R^{11} is, at each occurrence, independently H or C_1-C_4 alkyl;

X is -C(=O)-, -S-, -S(=O)-, or $-S(=O)_2-$;

Y is -C(=O)- or $-S(=O)_2-$;

Z is C_1-C_4 haloalkyl,
C_1-C_4 alkyl substituted with 0-3 Z^a,
C_2-C_4 alkenyl substituted with 0-3 Z^a,
C_2-C_4 alkynyl substituted with 0-3 Z^a,
C_3-C_{10} cycloalkyl substituted with 0-5 Z^b,

C_3-C_{10} carbocyle substituted with 0-5 Z^b,
aryl substituted with 0-5 Z^b, or
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl; said heterocyclic group substituted with 0-4 Z^b;

Z^a is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy,

C_3-C_{10} cycloalkyl substituted with 0-5 Z^b,
C_3-C_{10} carbocyle substituted with 0-5 Z^b,
aryl substituted with 0-5 Z^b, or
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,

morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl; said heterocyclic group substituted with 0-4 Z^b;

Z^b is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy,

C_3-C_{10} cycloalkyl substituted with 0-5 Z^c,
C_3-C_{10} carbocyle substituted with 0-5 Z^c,
aryl substituted with 0-5 Z^c, or
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl,

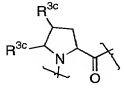
tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl; said heterocyclic group substituted with 0-4 Z^c;

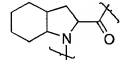
Z^c is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$, $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{20} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

alternatively, $NR^{20}R^{20}$ may form a piperidinyl, piperazinyl, or morpholinyl group;

A^2 is a bond, $-NH-CR^3R^4-C(=O)-$, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, Val,



or


;

A^3 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

A^4 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

R^1 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-3 R^{1a},
C_2-C_6 alkenyl substituted with 0-3 R^{1a},
C_2-C_6 alkynyl substituted with 0-3 R^{1a}, and
C_3-C_6 cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:
Cl, F, Br, I, CF_3, CHF_2, OH, =O, SH, $-CO_2R^{1b}$, $-SO_2R^{1b}$, $-SO_3R^{1b}$, $-P(O)_2R^{1b}$, $-P(O)_3R^{1b}$, $-C(=O)NHR^{1b}$, $-NHC(=O)R^{1b}$, $-SO_2NHR^{1b}$, $-OR^{1b}$, $-SR^{1b}$, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, $-S-(C_1-C_6$ alkyl),
aryl substituted with 0-5 R^{1c},
$-O-(CH_2)_q$-aryl substituted with 0-5 R^{1c},
$-S-(CH_2)_q$-aryl substituted with 0-5 R^{1c}, and
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl; and substituted with 0-3 R^{1c};

R^{1b} is H,
C_1-C_4 alkyl substituted with 0-3 R^{1c},
C_2-C_4 alkenyl substituted with 0-3 R^{1c},
C_2-C_4 alkynyl substituted with 0-3 R^{1c},
C_3-C_6 cycloalkyl substituted with 0-5 R^{1c},
C_3-C_6 carbocyle substituted with 0-5 R^{1c},
aryl substituted with 0-5 R^{1c}, or
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl; said heterocyclic group substituted with 0-3 R^{1c};

R^{1c} is selected at each occurrence from: C_1-C_4 alkyl, Cl, F, Br, I, OH, C_1-C_4 alkoxy, -CN, $-NO_2$, $C(O)OR^{1d}$, $NR^{1d}R^{1d}$, CF_3, and OCF_3;

R^{1d} is H or C_1-C_4 alkyl;

R^2 is H or C_1-C_4 alkyl;

R^3 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-4 R^{3a},
C_2-C_6 alkenyl substituted with 0-4 R^{3a},
C_2-C_6 alkynyl substituted with 0-4 R^{3a},
$-(CH_2)_q-$ C_3-C_6 cycloalkyl substituted with 0-4 R^{3b},
$-(CH_2)_q$-aryl substituted with 0-5 R^{3b}, and
$-(CH_2)_q$-5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl,

pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl; and said heterocyclic group is substituted with 0-2 R^{3b};

R^{3a} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with R^{10b};

R^{3b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{3c} is, at each occurrence, independently selected from: H, C_1-C_6 alkyl, -OH, and OR^{3d};

R^{3d} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_q$- C_3-C_6 cycloalkyl, $-(CH_2)_q$-aryl, or $-(CH_2)_q$-(5-10 membered heterocyclic group), wherein said heterocyclic group consists of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N;

R^4 is selected from the group: H, C_1-C_6 alkyl, phenyl, phenylmethyl-, phenylethyl-, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl-, and C_3-C_6 cycloalkylethyl-;

R^9 is selected from $-S(=O)_2R^{9a}$ and $-C(=O)R^{9a}$;

R^{9a} is selected from the group:
phenyl substituted with 0-3 R^{9c},
naphthyl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl; and said heterocyclic group is substituted with 0-3 R^{9c};

R^{9c} is selected at each occurrence from the group:
CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, NO_2;
C_1-C_4 alkyl substituted with 0-3 R^{9d},
C_1-C_4 alkoxy substituted with 0-3 R^{9d},
C_3-C_6 cycloalkyl substituted with 0-3 R^{9d},
aryl substituted with 0-5 R^{9d}, and
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl,

pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl; said heterocyclic group is substituted with 0-4 R^{9d};

R^{9d} is selected at each occurrence from the group: C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, and NO_2;

p is 1 or 2; and

q, at each occurence, is independently 0, 1 or 2.

[6] In a further even more preferred embodiment, the present invention provides novel compounds of Formula III, wherein:

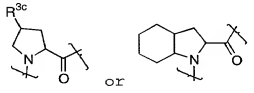
X is -C(=O)-;

Y is $-S(=O)_2-$;

Z is selected from the group:
methyl, ethyl, propyl, trifluoromethyl, phenyl, benzyl, 4-phenyl-phenyl, 4-NCS-phenyl, 2-fluorophenyl-, 3-fluorophenyl-, 4-fluorophenyl-, 2-chlorophenyl-, 3-chlorophenyl-, 4-chlorophenyl-, 2-cyanophenyl-, 3-cyanophenyl-, 4-cyanophenyl-, 2-nitrophenyl-, 3-nitrophenyl-, 4-nitrophenyl-, $2-CF_3SO_2$-phenyl-, $3-CF_3SO_2$-phenyl-, $4-CF_3SO_2$-phenyl-, $2-CF_3$-phenyl-, $3-CF_3$-phenyl-, $4-CF_3$-phenyl-, $3-NO_2-4-Cl$-phenyl-, $3-Cl-4-CH_3$-phenyl-, $2-Cl-5-CF_3$-phenyl-, $2-Cl-5-CO_2H$-phenyl-, $3-NO_2-4-CH_3$-phenyl-, $3-Cl-5-NH_2SO_2$-phenyl-, 3,5-diCF_3-phenyl-, 3,4-diCF_3-phenyl-,

3,5-diCl-phenyl-, 2,5-diCl-phenyl-, 3,4-diCl-phenyl-, 3,5-diF-phenyl-, 2,5-diF-phenyl-, 3,4-diF-phenyl-, 2-F-4-Cl-5-CO_2H-phenyl-, 2,4-diCl-5-CO_2H-phenyl-, 2,4-diCl-5-CH_3CO_2-phenyl-, 2,4-diCl-5-CH_3-phenyl-, 2-OH-3,5-diCl-phenyl-, 2,4,5-triCl-phenyl-, 3,5-diCl-4-(4-NO_2phenyl)phenyl-, 2-Cl-5-benzylNHCO-phenyl-, 2-Cl-5-CF_3CH_2NHCO-phenyl-, 2-Cl-5-cyclopropylmethylNHCO-phenyl-, 2-Cl-4-CH_3CONH-phenyl-, 3-Cl-5-(phenylCONHSO_2)-phenyl-, 3-Cl-5-CH_3CONH-phenyl-, 5-ethoxy-benzothiazol-2-yl, naphth-2-yl, (CH_3CONH)thiadiazolyl-, (s-butylCONH)thiadiazolyl-, (n-pentylCONH)thiadiazolyl-, (phenylCONH)thiadiazolyl-, and (3-ClphenylCONH)thiadiazolyl-;

A^2 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, Val;



;

A^3 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

A^3 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

R^1 is selected from the group:

$-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2CH_2C(CH_3)_3$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2CH_2CH_2CH_3$,

$-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH_2CH_2CH_3$,
$-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$,
$-CH_2CHF_2$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2CHF_2$,
$-CH=CH_2$, $-CH_2CH=CH_2$, $-CH=CHCH_3$, cis-$CH_2CH=CH(CH_3)$,
trans-$CH_2CH=CH(CH_3)$, $-CH_2CH_2CH=CH$, $-CH_2CH=C(CH_3)_2$,
$-CH_2CH_2CH=C(CH_3)_2$,
$-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CO_2C(CH_3)_3$,
$-CH_2CH_2CO_2C(CH_3)_3$, $-CH_2CH_2CH_2CH_2NH_2$,
phenyl, benzyl, phenethyl, phenpropyl, phenbutyl,
(2-methylphenyl)ethyl-, (3-methylphenyl)ethyl-,
(4-methylphenyl)ethyl-, (4-ethylphenyl)ethyl-,
(4-i-propylphenyl)ethyl-, (4-t-butylphenyl)ethyl-,
(4-hydroxyphenyl)ethyl-, (4-phenyl-phenyl)ethyl-,
(4-phenoxy-phenyl)ethyl-, (4-cyclohexyl-phenyl)ethyl-,
(4-cyclopropyl-phenyl)ethyl-,
(2,5-dimethylphenyl)ethyl-,
(2,4-dimethylphenyl)ethyl-, (2,6-difluorophenyl)ethyl-,
(4-cyclopentyl-phenyl)ethyl-,
(4-cyclobutyl-phenyl)ethyl-,
(2-trifluoromethylphenyl)ethyl-,
(3-trifluoromethylphenyl)ethyl-,
(4-trifluoromethylphenyl)ethyl-,
(2-fluorophenyl)ethyl-, (3-fluorophenyl)ethyl-,
(4-fluorophenyl)ethyl-, (2-chlorophenyl)ethyl-,
(3-chlorophenyl)ethyl-, (4-chlorophenyl)ethyl-,
(2-bromophenyl)ethyl-, (3-bromophenyl)ethyl-,
(4-bromophenyl)ethyl-,
(2,3,4,5,6-pentafluorophenyl)ethyl-
(naphth-2-yl)ethyl, (cyclobutyl)methyl,
(cyclobutyl)ethyl, (cyclobutyl)propyl, cyclopropyl,
cyclobutyl, cyclopentyl, and cyclohexyl;

R^2 is H, methyl or ethyl;

R^{3c} is H, methyl, ethyl, -OH, methoxy, ethoxy, propoxy,
phenoxy, or benzyloxy; and

R^9 is selected from:

2-pyrazinyl-carbonyl-,
4-(N-pyrrolyl)phenyl-carbonyl-,
5-(4-chlorophenyl)furan-2-yl-carbonyl-,
1-anthracenyl-carbonyl-,
7-nitro-anthracen-1-yl-carbonyl-,
(3-phenyl-2-cyanomethoxyphenyl)carbonyl-,
5-(2-Cl-3-CF_3-phenyl)-furan-2-yl-carbonyl-,
5-(4-Cl-phenyl)-furan-2-yl-carbonyl-,
5-(pyrid-2-yl)-thiophen-2-yl-carbonyl-,
(2-methoxyphenyl)ethylcarbonyl-,
(3-benzopyrrolyl)ethylcarbonyl-,
(N-phenyl-5-propyl-imidazol-4-yl)-carbonyl-,
1-naphthyl-sulphonyl-, and
5-(isoxazol-2-yl)thiophen-2-yl-sulphonyl-.

[7] In most preferred embodiment, the compound of Formula (I) is selected from the group:

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoylglycine;

(3S)-2-oxo-3-{[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino}-N-(2H-tetrazol-5-ylmethyl) pentanamide;

2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl]amino]-N-(sulfomethyl)pentanamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(2-nitrophenyl) sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(methylsulfonyl) glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(phenylmethyl) sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(phenylsulfonyl) glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(trifluoromethyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-nitrophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-nitrophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-fluorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-fluorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-fluorophenyl) sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chlorophenyl) sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentano yl-N-[(3-chlorophenyl) sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-(thionitroso) phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-(trifluoromethyl)phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-cyanophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3-chloro-4-methylphenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chloro-3-nitrophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L- isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichlorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-methyl-3-nitrophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-(trifluoromethyl)phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2,5-dichlorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,4-difluorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[(2,4;,5-trichlorophenyl)-sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(5-carboxy-4-chloro-2-fluorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(2-naphthalenylsulfonyl)glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L- alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[(4-(phenyl)phenyl)-sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(6-ethoxy-2-benzothiazolyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-[[(phenylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[[(2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L- alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[[(cyclopropylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-nitro-4-(2-pyrimidinylthio)phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-4-(acetylamino)phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-chloro-4-(2-benzoxazolylthio)phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[3,5-dichloro-4-(4-nitrophenoxy)phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-cyanophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[3-(aminosulfonyl)-5-chlorophenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[[3,5-bis(trifluoromethyl)phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[4-[5-[3-(4-chlorophenyl)-3-oxo-1-propenyl]-2-furanyl]phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[[(phenylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[[(2,2,2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[(benzoylamino)sulfonyl]-5-chlorophenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine;

(3S)-5,5-difluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)- L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N- (2H-tetrazol-5-ylmethyl)pentanamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)- 3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-(3-aminosulfonyl-5-chlorophenyl)sulfonyl]glycinamide;

(3S)-5,5,5-trifluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)- L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]- N-(2H-tetrazol-5-ylmethyl)pentanamide;

N-[4-*sec*-butyl-15-{[(3-chloro-5-{[(3,3,3-trifluoropropanoyl)amino]sulfonyl}phenyl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-[({3-chloro-5-[(hexanoylamino)sulfonyl]phenyl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[15-[([1,1'-biphenyl]-3-ylsulfonyl)amino]-4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-

hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-15-{[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide;

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-15-{[(3',5'-dichloro[1,1'-biphenyl]-4-yl)sulfonyl]amino}-10-ethyl-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-{[(4'-chloro[1,1'-biphenyl]-3-yl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-({[3-(2-methylphenoxy)phenyl]sulfonyl}amino)-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-({[3-(2-chlorophenoxy)phenyl]sulfonyl}amino)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13-pentaoxo-1-(2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid;

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-{[(4'-methyl[1,1'-biphenyl]-3-yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide;

N-[15-({[3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonyl}amino)-4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-[({5-[(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-[({5-[(2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[({5-[(4-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[({5-[(3-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[({5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-15-{[(3-phenoxyphenyl)sulfonyl]amino}-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide;

6-*sec*-butyl-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-1,4,7,10,13-pentaoxo-1-(2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid;

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[({5-[(3-methylbutanoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

methyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oate;

N-[4-*sec*-butyl-15-{[(3-chloro-5-{[(3-chlorobenzoyl)amino]sulfonyl}phenyl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-15-({[4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonyl}amino)-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[15-([1,1'-biphenyl]-3-ylsulfonyl)amino]-4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-[({5-[(4-*tert*-butylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-{[(3-chloro-5-{[(3-methylbutanoyl)amino]sulfonyl}phenyl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-14-[4-(4-methoxyphenyl)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-3-yl]-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide;

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-[({5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-15-[({5-[(3,5-difluorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-[({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide;

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-yn-1-yl}-2-pyrazinecarboxamide;

tert-butyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oate;

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-14-phenyl-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[((1*S*)-1-(cyclohexylmethyl)-2-{[(1*S*)-1-ethyl-2,3-dioxo-3-(1-pyrrolidinyl)propyl]amino}-2-oxoethyl)amino]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide;

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-15,15,15-trifluoro-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

N-{(1*S*,4*S*,7*S*,10*S*)-15-amino-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

(3*S*,6*S*,9*S*,12*S*,16*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-16-methyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oic acid;

N-[9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-2,5,8,11,14-pentaoxo-14-(2-pyrazinyl)-4,7,10,13-tetraazatetradec-1-anoyl]aspartic acid;

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaoctadecan-18-oic acid;

1,1-dimethylethyl N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L- prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-di fluoro-2-oxo-(3S)-3-aminopentanoylglycine;

(4R)-1-[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl]- N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H)-tetrazol-5-yl methyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide;

(4R)-N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-3-methoxy-2,3-dioxopropyl]-4-(phenylmethoxy)-L-prolinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-carboxy-2-chlorophenyl)-sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-acetylamino)1,3,4-thiadiazol-2-yl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[3,5-dichlorophenyl) sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-

aminopentanoyl N-(4-methyl-3-nitrophenyl)sulfonyl]-glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-(3-carboxyl-4-chloro-2-fluorophenyl)sulfonyl]-glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-[(3-chloro-4-acetylamino)phenyl]sulfonyl]-glycinamide;

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[(2*S*,4*R*)-2-({[(1*S*)-3-({2-[({3-[(benzoylamino)sulfonyl]-5-chlorophenyl}sulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]amino}carbonyl)-4-(benzyloxy)pyrrolidinyl]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide;

tert-butyl ({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*)-3-methyl-2-({(2*S*)-3-methyl-2-[(2-pyrazinylcarbonyl)amino]butanoyl}amino)butanoyl]pyrrolidinyl}carbonyl)amino]-5,5-difluoro-2-oxopentanoyl}amino)acetate;

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[(2*S*,4*R*)-4-(benzyloxy)-2-({[(1*S*)-3-[(2-{[(3-chloro-4-methylphenyl)sulfonyl]amino}-2-oxoethyl)amino]-1-(2,2-difluoroethyl)-2,3-dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide;

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[(2*S*,4*R*)-4-(benzyloxy)-2-({[(1*S*)-3-({2-[({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-

methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide;

methyl ({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-methyl-2-({(2*S*)-4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]pyrrolidinyl}carbonyl)amino]-5,5-difluoro-2-oxopentanoyl}amino)acetate;

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[(2*S*,4*R*)-4-(benzyloxy)-2-({[(1*S*)-3-[(2-{[(2,4-dichloro-5-methylphenyl)sulfonyl]amino}-2-oxoethyl)amino]-1-(2,2-difluoroethyl)-2,3-dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide;

N-[(1*S*)-1-({[(1*S*,2*R*)-1-({(2*S*,4*R*)-4-(benzyloxy)-2-[({(1*S*)-1-(2,2-difluoroethyl)-3-[(2-{[(3,4-difluorophenyl)sulfonyl]amino}-2-oxoethyl)amino]-2,3-dioxopropyl}amino)carbonyl]pyrrolidinyl}carbonyl)-2-methylbutyl]amino}carbonyl)-3-methylbutyl]-2-pyrazinecarboxamide;

methyl 5-({[({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-methyl-2-({(2*S*)-4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]pyrrolidinyl}carbonyl)amino]-5,5-difluoro-2-oxopentanoyl}amino)acetyl]amino}sulfonyl)-2,4-dichlorobenzoate;

N-{(1*S*)-1-[({((1*S*,2*R*)-1-[({(2*S*,4*R*)-4-(benzyloxy)-2-{[({(1*S*)-1-(2,2-difluoroethyl)-3-{[2-({[4-(3,5-dimethyl-1-piperidinyl)-3-nitrophenyl]sulfonyl}amino)-2-oxoethyl]amino}-2,3-dioxopropyl)amino]carbonyl}pyrrolidinyl)carbonyl]-2-methylbutyl}amino)carbonyl]-3-methylbutyl}-2-pyrazinecarboxamide;

N-[(1*S*)-1-({[(1*S*,2*R*)-1-({(2*S*,4*R*)-4-(benzyloxy)-2-[({(1*S*)-1-(2,2-difluoroethyl)-3-[(2-{[(3-nitrophenyl)sulfonyl]amino}-2-oxoethyl)amino]-2,3-dioxopropyl}amino)carbonyl]pyrrolidinyl}carbonyl)-2-methylbutyl]amino}carbonyl)-3-methylbutyl]-2-pyrazinecarboxamide;

N-{(1*S*)-1-[({(1*S*,2*R*)-1-[(2*S*,4*R*)-4-(benzyloxy)-2-{[((1*S*)-1-(2,2-difluoroethyl)-3-{[2-({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-2,3-dioxopropyl)amino]carbonyl}pyrrolidinyl)carbonyl]-2-methylbutyl}amino)carbonyl]-3-methylbutyl}-2-pyrazinecarboxamide;

5-({[({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-methyl-2-({(2*S*)-4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]pyrrolidinyl}carbonyl)amino]-5,5-difluoro-2-oxopentanoyl}amino)acetyl]amino}sulfonyl)-2,4-dichlorobenzoic acid;

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoylglycine;

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(trifluoromethyl)sulfonyl]glycinamide;

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide;

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3-nitrophenyl)sulfonyl]glycinamide;

(4R)-1-[[5-(4-chlorophenyl)-2-furanyl]carbonyl-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H-tetrazol-5-ylmethyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide;

(2*S*,4*R*)-4-(benzyloxy)-*N*-{(1*S*)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2*H*-tetraazol-5-ylmethyl)amino]propyl}-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

tert-butyl {[(3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetate;

{[(3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetic acid;

(2*S*,4*R*)-*N*-[(1*S*)-3-{[2-({[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

(2*S*,4*R*)-4-(benzyloxy)-*N*-((1*S*)-1-(2,2-difluoroethyl)-3-{[2-({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-2,3-dioxopropyl)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

((2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[({5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-1-(2,2-difluoroethyl)-3-({2-[({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2-oxoethyl}amino)-2,3-dioxopropyl]-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

tert-butyl {[(3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetate;

{[(3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetic acid;

(2*S*,4*R*)-*N*-[(1*S*)-3-{[2-({[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide;

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide;

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[([1,1'-biphenyl]-3-ylsulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide;

N-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide;

(6*S*,9*S*,12*S*)-*N*,3-diallyl-6-(cyclohexylmethyl)-12-isobutyl-9-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-tetraazahexadecan-1-amide;

(4*S*,7*S*,10*S*)-*N*,13-diallyl-10-(cyclohexylmethyl)-4-isobutyl-7-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-3,6,9,12-tetraazapentadecan-15-amide;

N-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-2-pyridinecarboxamide;

N-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}nicotinamide;

N-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-4-nitro-1*H*-pyrazole-3-carboxamide;

2-{(3*S*,6*S*,9*S*)-12-allyl-9-(cyclohexylmethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-4,7,10,13,14-pentaoxo-2,5,8,11,15-pentaazaoctadec-17-en-1-anoyl}benzoic acid;

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl]nicotinamide;

N-allyl-9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-tetraazahexadecan-1-amide;

({3-[({1-[3-methyl-2-({4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]-octahydro-1*H*-indol-2-yl}carbonyl)amino]-2-oxopentanoyl}amino)acetic acid;

tert-butyl ({3-[({1-[3-methyl-2-({4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)-pentanoyl]octahydro-1*H*-indol-2-yl}carbonyl)amino]-2-oxopentanoyl}amino)acetate; and

(3*S*,6*S*,9*S*,12*S*)-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-9-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-tetraazahexadecan-1-oic acid;

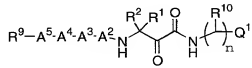
or a pharmaceutically acceptable salt form thereof.

[8] In another preferred embodiment, the present invention provides novel compounds of Formula I, wherein:

Q is $-(CR^{10}R^{10c})_n-Q^1$ or

an amino acid residue, wherein the amino acid residue comprises a natural, a modified or an unnatural amino acid.

[9] In a more preferred embodiment, the present invention provides novel compounds of Formula IIb, wherein:



(IIb)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

R^{10} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, and C_1-C_6 alkyl substituted with 0-1 R^{10a};

R^{10a} is selected from the group: halo, $-NO_2$, $-CN$, $-CF_3$, $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with 0-1 R^{10b};

R^{10b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{10c} is H or C_1-C_4 alkyl;

alternatively, R^{10} and R^{10c} can be combined to form a C_3-C_6 cycloalkyl group substituted with 0-1 R^{10a};

R^{11} is, at each occurrence, independently H or C_1-C_4 alkyl;

R^{11a} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

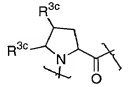
Q^1 is selected from:
$-CO_2R^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-P(O)_2R^{11}$, $-P(O)_3R^{11}$,
aryl substituted with 0-4 Q^{1a}, and
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Q^{1a};

Q^{1a} is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{19}$, $-C(=O)NR^{19}R^{19}$, $-NHC(=O)R^{19}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{19}$, $-NR^{19}R^{19}$, $-OR^{19}$, $-SR^{19}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{19} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, aryl(C_1-C_4 alkyl), C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl);

alternatively, $NR^{19}R^{19}$ may form a 5-6 membered heterocyclic group consisting of carbon atoms, a nitrogen atom, and optionally a second heteroatom selected from the group: O, S, and N;

A^2 is a bond, -NH-CR^3R^4-C(=O)-, an amino acid residue,



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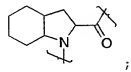


;

A^3 is a bond, -NH-CR^5R^6-C(=O)-, or an amino acid residue;

A^4 is a bond, -NH-CR^7R^8-C(=O)-, or an amino acid residue;

A^5 is a bond or an amino acid residue;

A^7 is a bond or an amino acid residue;

A^8 is an amino acid residue;

A^9 is an amino acid residue;

R^1 is selected from the group: H, F,
C_1-C_6 alkyl substituted with 0-3 R^{1a},
C_2-C_6 alkenyl substituted with 0-3 R^{1a},
C_2-C_6 alkynyl substituted with 0-3 R^{1a}, and
C_3-C_6 cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:
Cl, F, Br, I, CF_3, CHF_2, OH, =O, SH,
-CO_2R^{1b}, -SO_2R^{1b}, -SO_3R^{1b}, -$P(O)_2R^{1b}$, -$P(O)_3R^{1b}$,
-C(=O)NHR^{1b}, -$NHC(=O)R^{1b}$, -SO_2NHR^{1b}, -OR^{1b}, -SR^{1b},
C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy,
-S-(C_1-C_6 alkyl),
aryl substituted with 0-5 R^{1c},
-O-$(CH_2)_q$-aryl substituted with 0-5 R^{1c},
-S-$(CH_2)_q$-aryl substituted with 0-5 R^{1c}, and

5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and substituted with 0-3 R^{1c};

R^{1b} is H,
C_1-C_4 alkyl substituted with 0-3 R^{1c},
C_2-C_4 alkenyl substituted with 0-3 R^{1c},
C_2-C_4 alkynyl substituted with 0-3 R^{1c},
C_3-C_6 cycloalkyl substituted with 0-5 R^{1c},
C_3-C_6 carbocyle substituted with 0-5 R^{1c},
aryl substituted with 0-5 R^{1c}, or
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 R^{1c};

R^{1c} is selected at each occurrence from: C_1-C_4 alkyl, Cl, F, Br, I, OH, C_1-C_4 alkoxy, -CN, $-NO_2$, $C(O)OR^{1d}$, $NR^{1d}R^{1d}$, CF_3, and OCF_3;

R^{1d} is H or C_1-C_4 alkyl;

R^2 is H, F, or C_1-C_4 alkyl;

R^3 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-4 R^{3a},
C_2-C_6 alkenyl substituted with 0-4 R^{3a},
C_2-C_6 alkynyl substituted with 0-4 R^{3a},
$-(CH_2)_q$- C_3-C_6 cycloalkyl substituted with 0-4 R^{3b},
$-(CH_2)_q$-aryl substituted with 0-5 R^{3b}, and
$-(CH_2)_q$-5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-2 R^{3b};

R^{3a} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with R^{10b};

R^{3b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{3c} is, at each occurrence, independently selected from: H, C_1-C_6 alkyl, -OH, and OR^{3d};

R^{3d} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_q$- C_3-C_6 cycloalkyl, $-(CH_2)_q$-aryl, or $-(CH_2)_q$-(5-10 membered heterocyclic group), wherein said heterocyclic group consists of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N;

R^4 is selected from the group: H, C_1-C_6 alkyl, phenyl, phenylmethyl-, phenylethyl-, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl-, and C_3-C_6 cycloalkylethyl-;

R^5 and R^7 are independently H or R^3;

R^6 and R^8 are independently H or R^4;

R^9 is selected from the group: $-S(=O)R^{9a}$, $-S(=O)_2R^{9a}$, $-C(=O)R^{9a}$, $-C(=O)OR^{9a}$, $-C(=O)NHR^{9a}$, C_1-C_3 alkyl-R^{9a}, C_2-C_6 alkenyl-R^{9a}, and C_2-C_6 alkynyl-R^{9a};

R^{9a} is selected from the group:
C_1-C_6 alkyl substituted with 0-3 R^{9b},
C_3-C_6 cycloalkyl substituted with 0-3 R^{9c},
aryl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the

group: O, S, and N, and said heterocyclic group is substituted with 0-3 R^{9c};

R^{9b} is selected from the group: phenyl, naphthyl, benzyl, and 5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and R^{9b} is substituted with 0-3 R^{9c};

R^{9c} is selected at each occurrence from the group:
CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, NO_2;
C_1-C_4 alkyl substituted with 0-3 R^{9d},
C_1-C_4 alkoxy substituted with 0-3 R^{9d},
C_3-C_6 cycloalkyl substituted with 0-3 R^{9d},
aryl substituted with 0-5 R^{9d}, and
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-4 R^{9d};

R^{9d} is selected at each occurrence from the group:
C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, and NO_2;

n is 1, 2, or 3; and

p is 1 or 2; and

q, at each occurence, is independently 0, 1 or 2.

[10] In a further more preferred embodiment, the present invention provides novel compounds of Formula IIb, wherein:

R^{10} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, and C_1-C_6 alkyl substituted with 0-1 R^{10a};

R^{10a} is selected from the group: halo, $-NO_2$, $-CN$, $-CF_3$, $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with 0-1 R^{10b};

R^{10b} is selected from the group: $-CO_2H$, $-NH_2$, $-OH$, $-SH$, and $-C(=NH)NH_2$;

R^{10c} is H or C_1-C_4 alkyl;

alternatively, R^{10} and R^{10c} can be combined to form a C_3-C_6 cycloalkyl group substituted with 0-1 R^{10a};

R^{11} is, at each occurrence, independently H or C_1-C_4 alkyl;

R^{11a} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

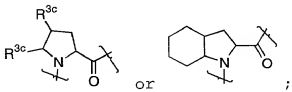
Q^1 is selected from:
$-CO_2R^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-P(O)_2R^{11}$, $-P(O)_3R^{11}$,
aryl substituted with 0-4 Q^{1a}, and
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Q^{1a};

Q^{1a} is H, F, Cl, Br, I, $-NO_2$, $-CN$, $-NCS$, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{19}$, $-C(=O)NR^{19}R^{19}$, $-NHC(=O)R^{19}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{19}$, $-NR^{19}R^{19}$, $-OR^{19}$, $-SR^{19}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{19} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, aryl(C_1-C_4 alkyl), C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl);

alternatively, $NR^{19}R^{19}$ may form a piperidinyl, piperazinyl, or morpholinyl group;

A^2 is a bond, -NH-CR^3R^4-C(=O)-, an amino acid residue,



;

A^3 is a bond or an amino acid residue;

A^4 is a bond or an amino acid residue;

A^5 is a bond;

R^1 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-3 R^{1a},
C_2-C_6 alkenyl substituted with 0-3 R^{1a},
C_2-C_6 alkynyl substituted with 0-3 R^{1a}, and
C_3-C_6 cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:
Cl, F, Br, I, CF_3, CHF_2, OH, =O, SH,
$-CO_2R^{1b}$, $-SO_2R^{1b}$, $-SO_3R^{1b}$, $-P(O)_2R^{1b}$, $-P(O)_3R^{1b}$,
$-C(=O)NHR^{1b}$, $-NHC(=O)R^{1b}$, $-SO_2NHR^{1b}$, $-OR^{1b}$, $-SR^{1b}$,
C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy,
-S-(C_1-C_6 alkyl),
aryl substituted with 0-5 R^{1c},
$-O-(CH_2)_q$-aryl substituted with 0-5 R^{1c},
$-S-(CH_2)_q$-aryl substituted with 0-5 R^{1c}, and

5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and substituted with 0-3 R^{1c};

R^{1b} is H,
C_1-C_4 alkyl substituted with 0-3 R^{1c},
C_2-C_4 alkenyl substituted with 0-3 R^{1c},
C_2-C_4 alkynyl substituted with 0-3 R^{1c},
C_3-C_6 cycloalkyl substituted with 0-5 R^{1c},
C_3-C_6 carbocyle substituted with 0-5 R^{1c},
aryl substituted with 0-5 R^{1c}, or
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 R^{1c};

R^{1c} is selected at each occurrence from: C_1-C_4 alkyl, Cl, F, Br, I, OH, C_1-C_4 alkoxy, -CN, $-NO_2$, $C(O)OR^{1d}$, $NR^{1d}R^{1d}$, CF_3, and OCF_3;

R^{1d} is H or C_1-C_4 alkyl;

R^2 is H or C_1-C_4 alkyl;

R^3 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-4 R^{3a},
C_2-C_6 alkenyl substituted with 0-4 R^{3a},
C_2-C_6 alkynyl substituted with 0-4 R^{3a},
$-(CH_2)_q$- C_3-C_6 cycloalkyl substituted with 0-4 R^{3b},
$-(CH_2)_q$-aryl substituted with 0-5 R^{3b}, and
$-(CH_2)_q$-5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-2 R^{3b};

R^{3a} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with R^{10b};

R^{3b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{3c} is, at each occurrence, independently selected from: H, C_1-C_6 alkyl, -OH, and OR^{3d};

R^{3d} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_q$- C_3-C_6 cycloalkyl, $-(CH_2)_q$-aryl, or $-(CH_2)_q$-(5-10 membered heterocyclic group), wherein said heterocyclic group consists of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N;

R^4 is selected from the group: H, C_1-C_6 alkyl, phenyl, phenylmethyl-, phenylethyl-, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl-, and C_3-C_6 cycloalkylethyl-;

R^9 is selected from the group: $-S(=O)_2R^{9a}$, $-C(=O)R^{9a}$, C_1-C_3 alkyl-R^{9a}, C_2-C_6 alkenyl-R^{9a}, and C_2-C_6 alkynyl-R^{9a};

R^{9a} is selected from the group:
C_1-C_6 alkyl substituted with 0-3 R^{9b},
C_3-C_6 cycloalkyl substituted with 0-3 R^{9c},
aryl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-3 R^{9c};

R^{9b} is selected from the group: phenyl, naphthyl, benzyl, and 5-10 membered heterocyclic group consisting of

carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and R^{9b} is substituted with 0-3 R^{9c};

R^{9c} is selected at each occurrence from the group:
CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, NO_2;
C_1-C_4 alkyl substituted with 0-3 R^{9d},
C_1-C_4 alkoxy substituted with 0-3 R^{9d},
C_3-C_6 cycloalkyl substituted with 0-3 R^{9d},
aryl substituted with 0-5 R^{9d}, and
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-4 R^{9d};

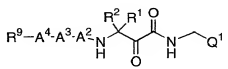
R^{9d} is selected at each occurrence from the group:
C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, and NO_2;

n is 1 or 2; and

p is 1 or 2; and

q, at each occurence, is independently 0, 1 or 2.

[11] In an even more preferred embodiment, the present invention provides novel compounds of Formula IIIb, wherein:



(IIIb)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

Q^1 is selected from:

$-CO_2R^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-P(O)_2R^{11}$, $-P(O)_3R^{11}$,

aryl substituted with 0-4 Q^{1a}, and

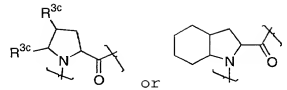
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl; said heterocyclic group substituted with 0-4 Q^{1a};

Q^{1a} is H, F, Cl, Br, I, $-NO_2$, -CN, -NCS, $-CF_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-CO_2R^{19}$, $-C(=O)NR^{19}R^{19}$, $-NHC(=O)R^{19}$, $-SO_2R^{19}$, $-SO_2NR^{19}R^{19}$, $-NR^{19}R^{19}$, $-OR^{19}$, $-SR^{19}$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{19} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, aryl(C_1-C_4 alkyl), C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl);

alternatively, $NR^{19}R^{19}$ may form a piperidinyl, piperazinyl, or morpholinyl group;

A^2 is a bond, $-NH-CR^3R^4-C(=O)-$, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, Val,



A^3 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

A^4 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

R^1 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-3 R^{1a},
C_2-C_6 alkenyl substituted with 0-3 R^{1a},
C_2-C_6 alkynyl substituted with 0-3 R^{1a}, and
C_3-C_6 cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:
Cl, F, Br, I, CF_3, CHF_2, OH, =O, SH,
$-CO_2R^{1b}$, $-SO_2R^{1b}$, $-SO_3R^{1b}$, $-P(O)_2R^{1b}$, $-P(O)_3R^{1b}$,
$-C(=O)NHR^{1b}$, $-NHC(=O)R^{1b}$, $-SO_2NHR^{1b}$, $-OR^{1b}$, $-SR^{1b}$,
C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy,
$-S-(C_1$-C_6 alkyl),
aryl substituted with 0-5 R^{1c},
$-O-(CH_2)_q$-aryl substituted with 0-5 R^{1c},
$-S-(CH_2)_q$-aryl substituted with 0-5 R^{1c}, and
5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl,

1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl; and substituted with 0-3 R^{1c};

R^{1b} is H,

C_1-C_4 alkyl substituted with 0-3 R^{1c},

C_2-C_4 alkenyl substituted with 0-3 R^{1c},

C_2-C_4 alkynyl substituted with 0-3 R^{1c},

C_3-C_6 cycloalkyl substituted with 0-5 R^{1c},

C_3-C_6 carbocyle substituted with 0-5 R^{1c},

aryl substituted with 0-5 R^{1c}, or

5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl; said heterocyclic group substituted with 0-4 R^{1c};

R^{1c} is selected at each occurrence from: C_1-C_4 alkyl, Cl, F, Br, I, OH, C_1-C_4 alkoxy, -CN, $-NO_2$, $C(O)OR^{1d}$, $NR^{1d}R^{1d}$, CF_3, and OCF_3;

R^{1d} is H or C_1-C_4 alkyl;

R^2 is H or C_1-C_4 alkyl;

R^3 is selected from the group: H,
C_1-C_6 alkyl substituted with 0-4 R^{3a},
C_2-C_6 alkenyl substituted with 0-4 R^{3a},
C_2-C_6 alkynyl substituted with 0-4 R^{3a},
-$(CH_2)_q$- C_3-C_6 cycloalkyl substituted with 0-4 R^{3b},
-$(CH_2)_q$-aryl substituted with 0-5 R^{3b}, and
-$(CH_2)_q$-5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl; and said heterocyclic group is substituted with 0-2 R^{3b};

R^{3a} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with R^{10b};

R^{3b} is selected from the group: $-CO_2H$, $-NH_2$, -OH, -SH, and $-C(=NH)NH_2$;

R^{3c} is, at each occurrence, independently selected from: H, C_1-C_6 alkyl, -OH, and OR^{3d};

R^{3d} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

$-(CH_2)_q-$ C_3-C_6 cycloalkyl, $-(CH_2)_q$-aryl, or $-(CH_2)_q$-(5-10 membered heterocyclic group), wherein said heterocyclic group consists of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N;

R^4 is selected from the group: H, C_1-C_6 alkyl, phenyl, phenylmethyl-, phenylethyl-, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl-, and C_3-C_6 cycloalkylethyl-;

R^9 is selected from $-S(=O)_2R^{9a}$ and $-C(=O)R^{9a}$;

R^{9a} is selected from the group:
phenyl substituted with 0-3 R^{9c},
naphthyl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl; and said heterocyclic group is substituted with 0-3 R^{9c};

R^{9c} is selected at each occurrence from the group:

CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, NO_2;

C_1-C_4 alkyl substituted with 0-3 R^{9d},

C_1-C_4 alkoxy substituted with 0-3 R^{9d},

C_3-C_6 cycloalkyl substituted with 0-3 R^{9d},

aryl substituted with 0-5 R^{9d}, and

5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl; and said heterocyclic group is substituted with 0-4 R^{9d};

R^{9d} is selected at each occurrence from the group:
C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, -CN, and NO_2;

p is 1 or 2; and

q, at each occurence, is independently 0, 1 or 2.

In another embodiment, the present invention provides a novel pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula (I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating HCV infection which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Formula

(I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides novel compounds of Formula (I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt forms thereof for use in therapy.

In another embodiment, the present invention provides the use of novel compounds of Formula (I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt forms thereof for the manufacture of a medicament for the treatment of HCV.

DEFINITIONS

The compounds herein described have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Geometric isomers of double bonds such as olefins and C=N double bonds can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that

the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (i.e., within) of the ring.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R^{1a}) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R^{1a}, then said group may optionally be substituted with up to three R^{1a} groups and R^{1a} at each occurrence is selected independently from the definition of R^{1a}. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of

carbon atoms. For example, "C_1-C_{10} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration having the specified number of carbon atoms and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain. For example, "C_2-C_6 alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more carbon-carbon triple bonds which may occur in any stable point along the chain. For example, "C_2-C_6 alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

"Cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. For example, "C_3-C_6 cycloalkyl" denotes such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

"Alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_1-C_6 alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and

s-pentoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

"Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" which is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

As used herein, "carbocycle" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 5, 6, or 7- membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, 13, or 14-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (ie. aromatic or "heteroaryl"), and which consists of carbon

atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized to -NO-, -SO-, or $-SO_2-$. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 2-pyrrolidonyl, 2*H*,6*H*-1,5,2-dithiazinyl, 2*H*-pyrrolyl, 3*H*-indolyl, 4-piperidonyl, 4*H*-quinolizinyl, 6*H*-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4a*H*-carbazolyl, β-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, imidazolopyridinyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl,

phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thiazolopyridinyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

Preferred 5 to 10 membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

Preferred 5 to 6 membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and

triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "aryl", "C_6-C_{10} aryl" or "aromatic residue", is intended to mean an aromatic moiety containing, if specified, the specified number of carbon atoms. For example, aryl is phenyl, pyridinyl or naphthyl. Unless otherwise specified, "aryl", "C_6-C_{10} aryl" or "aromatic residue" may be unsubstituted or substituted with 0 to 3 groups selected from H, OH, OCH_3, Cl, F, Br, I, CN, NO_2, NH_2, $N(CH_3)H$, $N(CH_3)_2$, CF_3, OCF_3, $C(=O)CH_3$, SCH_3, $S(=O)CH_3$, $S(=O)_2CH_3$, CH_3, CH_2CH_3, CO_2H, and CO_2CH_3.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are natural amino acids (e.g., L-amino acids), modified and unusual amino acids (e.g., D-amino acids), as well as amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids, such as those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. "Natural amino acids" include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tyrosine, tyrosine, tryptophan, proline, and valine. Natural non-protein amino acids include, but are not limited to arginosuccinic acid, citrulline, cysteine sulfinic acid, 3,4-dihydroxyphenylalanine, homocysteine, homoserine, ornithine, 3-monoiodotyrosine, 3,5-diiodotryosine, 3,5,5'-triiodothyronine, and 3,3',5,5'-tetraiodothyronine. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-CBZ-protected amino acid, 2,4-diaminobutyric acid,

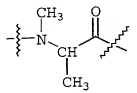
homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine, ß-phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

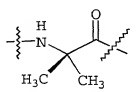
As used throughout the specification, the following abbreviations for amino acid residues or amino acids apply:

Abu is L-aminobutyric acid;
Ala is L-alanine;
Alg is L-2-amino-4-pentenoic acid;
Ape is L-2-aminopentanoic acid;
Arg is L-arginine;
Asn is L-asparagine;
Asp is L-aspartic acid;
Aze is azedine-2-carboxlic acid;
Cha is L-2-amino-3-cyclohexylpropionic acid;
Cpa is L-2-amino-3-cyclopropylpropionic acid
Cpg is L-2-amino-2-cyclopropylacetic acid;
Cys is L-cysteine;
Dfb is L-4,4'-difluoro-1-amino-butyric acid;
Dpa is L-2-amino-3,3-diphenylpropionic acid
Gln is L-glutamine;
Glu is L-glutamic acid;
Gly is glycine;
His is L-histidine;
HomoLys is L-homolysine;
Hyp is L-4-hydroxyproline;
Ile is L-isoleucine;
Irg is isothiouronium analog of L-Arg;
Leu is L-leucine;
Lys is L-lysine;

Met is L-methionine;
Orn is L-ornithine;
Phe is L-phenylalanine;
Phe(4-fluoro) is para-fluorophenylalanine;
Pro is L-proline;
Sar is L-sarcosine;
Ser is L-serine;
Thr is L-threonine;
Tpa is L-2-amino-5,5,5-trifluoropentanoic acid;
Trp is L-tryptophan;
Tyr is L-tyrosine;
Val is L-valine; and
HyPOBn: O-benzyl hydroxylproline.

"Amino acid residue" as used herein, refers to natural, modified or unnatural amino acids of either D- or L-configuration and means an organic compound containing both a basic amino group and an acidic carboxyl group. Natural amino acids residues are Ala, Arg, Asn, Asp, Aze, Cys, Gln, Glu, Gly, His, Hyp, Ile, Irg Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, and Val. Roberts and Vellaccio, The Peptides, Vol 5; 341-449 (1983), Academic Press, New York, discloses numerous suitable unnatural amino acids and is incorporated herein by reference for that purpose. Additionally, said reference describes, but does not extensively list, acylic N-alkyl and acyclic α,α-disubstituted amino acids. Included in the scope of the present invention are N-alkyl, aryl, and alkylaryl analogs of both in chain and N-terminal amino acid residues. Similarly, alkyl, aryl, and alkylaryl maybe substituted for the alpha hydrogen. Illustrated below are examples of N-alkyl and alpha alkyl amino acid residues, respectively.





Unnatural amino acids that fall within the scope of this invention are by way of example and without limitation:

2-aminobutanoicacid, 2-aminopentanoic acid, 2-aminohexanoic acid, 2-aminoheptanoicacid, 2-aminooctanoic acid, 2-aminononanoic acid, 2-aminodecanoic acid, 2-aminoundecanoic acid, 2-amino-3,3-dimethylbutanoic acid, 2-amino-4,4-dimethylpentanoic acid, 2-amino-3-methylhexanoic acid, 2-amino-3-methylheptanoic acid, 2-amino-3-methyloctanoic acid, 2-amino-3-methylnonanoic acid, 2-amino-4-methylhexanoic acid, 2-amino-3-ethylpentanoic acid, 2-amino-3,4-dimethylpentanoic acid, 2-amino-3,5-dimethylhexanoic acid, 2-amino-3,3-dimethylpentanoic acid, 2-amino-3-ethyl-3-methylpentanoic acid, 2-amino-3,3-diethylpentanoic acid, 2-amino-5-methylhexanoic acid, 2-amino-6-methylheptanoic, 2-amino-7-methyloctanoic, 2-amino-2-cyclopentylacetic, 2-amino-2-cylcohexylacetic acid, 2-amino-2-(1-methylcylcohexyl)acetic acid, 2-amino-2-(2-methyl-1-methylcylcohexyl)acetic acid, 2-amino-2-(3-methyl-1-methylcylcohexyl)acetic acid, 2-amino-2-(4-methyl-1-methylcylcohexyl)acetic acid, 2-amino-2-(1-ethylcycolhexyl)acetic acid, 2-amino-3-(cyclohexyl)propanoic acid, 2-amino-4-(cyclohexyl)butanoic acid, 2-amino-3-(1-adamantyl)propanoic acid, 2-amino-3-butenoic acid, 2-amino-3-methyl-3-butenoic acid, 2-amino-4-pentenoic acid, 2-amino-4-hexenoic acid, 2-amino-5-heptenoic acid, 2-amino-4-methyl-4-hexenoic acid, 2-amino-5-methyl-4-hexenoic acid, 2-amino-4-methy-5-hexenoic acid, 2-amino-6-heptenoic acid, 2-amino-3,3,4-trimethyl-4-pentenoic acid, 2-amino-4-chloro-4-pentenoic, 2-amino-4,4-dichloro-3-butenoic acid, 2-amino-3-(2-methylenecyclopropyl)-propanoic acid, 2-amino-2-(2-cyclopentenyl)acetic acid, 2-amino-2-(cyclohexenyl)acetic acid, 2-amino-3-(2-cyclopentenyl)propanoic acid, 2-amino-3-(3-cyclopentenyl)propanoic acid, 2-amino-3-(1-cyclohexyl)propanoic acid, 2-amino-2-(1-cyclopentenyl)acetic acid, 2-amino-2-(1-cylcohexyl)acetic

acid, 2-amino-2-(1-cylcoheptenyl)acetic acid, 2-amino-2-(1-cyclooctenyl)acetic acid, 2-amino-3-(1-cycloheptenyl)propanoic acid, 2-amino-3-(1,4-cyclohexadienyl)propanoic acid, 2-amino-3-(2,5-cyclohexadienyl)propanoic acid, 2-amino-2-(7-cycloheptatrienyl)acetic acid, 2-amino-4,5-hexadienoic acid, 2-amino-3-butynoic acid, 2-amino-4-pentyoic acid, 2-amino-4-hexynoic acid, 2-amino-4-hepten-6-ynoic acid, 2-amino-3-fluoropropanoic acid, 2-amino-3,3,3-trifluoropropanoic acid, 2-amino-3-fluorobutanoic acid, 2-amino-3-fluoropentanoic acid, 2-amino-3-fluorohexanoic acid, 2-amino-3,3-difluorobutanoic acid, 2-amino-3,3-difluoro-3-phenylpropanoic acid, 2-amino-3-perfluoroethylpropanoic acid, 2-amino-3-perfluoropropylpropanoic acid, 2-amino-3-fluoro-3-methylbutanoic acid, 2-amino-5,5,5-trifluoropentanoic acid, 2-amino-3-methyl-4,4,4-trifluorobutanoic acid, 2-amino-3-trifluoromethyl-4,4,4-trifluorobutanoic acid, 2-amino-3,3,4,4,5,5-heptafluoropentanoic acid, 2-amino-3-methyl-5-fluoropentanoic acid, 2-amino-3-methyl-4-fluoropentanoic acid, 2-amino-5,5-difluorohexanoic acid, 2-amino-4-(fluoromethyl)-5-fluoropentanoic acid, 2-amino-4-trifluoromethyl-5,5,5-trifluoropentanoic acid, 2-amino-3-fluoro-3-methylbutanoic acid, 2-amino-3-fluoro-3-phenylpentanoic acid, 2-amino-2-(1-fluorocyclopentyl)acetic acid, 2-amino-2-(1-fluorocyclohexyl)acetic acid, 2-amino-3-chloropropanoic acid acid, 2-amino-3-chlorobutanoic acid acid, 2-amino-4,4-dichlorobutanoic acid acid, 2-amino4,4,4-trichlorobutanoic acid, 2-amino-3,4,4-trichlorobutanoic acid, 2-amino-6-chlorohexanoic acid, 2-amino-4-bromobutanoic acid, 2-amino-3-bromobutanoic acid, 2-amino-3-mercaptobutanoic acid, 2-amino-4-mercaptobutanoic acid, 2-amino-3-mercapto-3,3-dimethylpropanoic acid, 2-amino-3-mercapto-3-methylpentanoic acid, 2-amino-3-mercaptopentanoic acid, 2-amino-3-mercapto-4-methylpentanoic acid, 2-amino-3-methyl-4-mercaptopentanoic acid, 2-amino-5-mercapto-5-methylhexanoic acid, 2-amino-2-(1-mercaptocyclobutyl)acetic acid, 2-amino-2-(1-

mercaptocyclopentyl)acetic acid, 2-amino-2-(1-mercaptocyclohexyl)acetic acid, 2-amino-5-(methylthio)pentanoic acid, 2-amino-6-(methylthio)hexanoic acid, 2-amino-4-methylthio-3-phenylbutanoic acid, 2-amino-5-ethylthio-5-methylpentanoic acid, 2-amino-5-ethylthio-3,5,5-trimethylpentanoic acid, 2-amino-5-ethylthio-5-phenylpentanoic acid, 2-amino-5-ethylthio-5-pentanoic acid, 2-amino-5-butylthio-5-methylpentanoic acid, 2-amino-5-butylthio-3,5,5-trimethylpentanoic acid, 2-amino-5-butylthio-5-phenylpentanoic acid, 2-amino-5-(butylthio)pentanoic acid, 2-amino-3-methy4-hydroselenopentanoic acid, 2-amino-4-methylselenobutanoic acid, 2-amino-4-ethylselenobutanoic acid, 2-amino-4-benzylselenobutanoic acid, 2-amino-3-methyl-4-(methylseleno)butanoic acid, 2-amino-3-(aminomethylseleno)propanoic acid, 2-amino-3-(3-aminopropylseleno)propanoic acid, 2-amino-4-methyltellurobutanoic acid, 2-amino-4-hydroxybutanoic acid, 2-amino-4-hydroxyhexanoic acid, 2-amino-3-hydroxypentanoic acid, 2-amino-3-hydroxyhexanoic acid, 2-amino-3methyl-4-hydroxybutanoic acid, 2-amino-3-hydroxy-3-methylbutanoic acid, 2-amino-6-hydroxyhexanoic acid, 2-amino-4-hydroxyhexanoic acid, 2-amino-3-hydroxy-4-methylpentanoic acid, 2-amino-3-hydroxy-3-methylpentanoic acid, 2-amino4-hydroxy-3,3-dimethylbutanoic acid, 2-amino-3-hydroxy4-methylpentanoic acid, 2-amino-3-hydroybutanedioic acid, 2-amino-3-hydroxy-3-phenyl-propanoic acid, 2-amino-3-hydroxy-3-(4-nitrophenyl)propanoic acid, 2-amino-3-hydroxy-3-(3-pyridyl)propanoic acid, 2-amino-2-(1-hydroxycyclopropyl)acetic acid, 2-amino-3-(1-hydroxycyclohexyl)propanoic acid, 2-amino-3-hydroxy-3-phenylpropanoic acid, 2-amino-3-hydroxy-3-[3-bis(2-chloroethyl)aminophenyl]propanoic acid, 2-amino-3-hydroxy-3-(3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-hydroxy-3-(3,4-methylenedioxyphenyl)propanoic acid, 2-amino-4-fluoro-3-hydroxybutanoic acid, 2-amino-4,4,4-trichloro-3-hydroxybutanoic acid, 2-amino-3-hydroxy-4-hexynoic acid, 2-amino-3,4-dihydroxybutanoic acid, 2-amino-3,4,5,6-

tetrahydroxyhexanoic acid, 2-amino-4,5-dihydroxy-3-methylpentanoic acid, 2-amino-5,6-dihydroxyhexanoic acid, 2-amino-5-hydroxy-4-(hydroxyrnethyl)pentanoic acid, 2-amino-4,5-dihydroxy-4-(hydroxymethyl)pentanoic acid, 2-amino-3-hydroxy-5-benzyloxypentanoic acid, 2-amino-3-(2-aminoethoxy)propanoic acid, 2-amino-4-(2-aminoethoxy)butanoic acid, 2-amino-4-oxobutanoic acid, 2-amino-3-oxobutanoic acid, 2-amino-4-methyl-3-oxopentanoic acid, 2-amino-3-phenyl-3-oxopropanoic acid, 2-amino-4-phenyl-3-oxobutanoic acid, 2-amino-3-methyl-4-oxopentanoic acid, 2-amino-4-oxo-4-(4-hydroxyphenyl)butanoic acid, 2-amino-4-oxo-4-(2-furyl)butanoic acid, 2-amino-4-oxo-4-(2-nitrophenyl)butanoic acid, 2-amino-4-oxo-4-(2-amino-4-chlorophenyl)butanoic acid, 2-amino-3-(4-oxo-1-cyclohexenyl)propanoic acid, 2-amino-3-(4-oxocyclohexanyl)propanoic acid, 2-amino-3-(2,5-dimethyl-3,6-dioxo-1,4-cydohexadienyl)propanoic acid, 2-amino-3-(1-hydroxy-5-methyl-7-oxo-cyclohepta-1,3,5-trien-2-yl)propanoic acid, 2-amino-3-(1-hydroxy-7-oxo-cyclohepta-1,3,5-trien-3-yl)propanoic acid, 2-amino-3-(1-hydroxy-7-oxo-cyclohepta-1,3,5-trien-4-yl)propanoic acid, 2-amino-4-methoxy-3-butenoic acid, 2-amino-4-(2-aminoethoxy)-3-butenoic acid, 2-amino-4-(2-amino-3-hydroxypropyl)-3-butenoic acid, 2-amino-2-(4-methoxy-1,4-cyclohexadienyl)acetic acid, 2-amino-3,3-diethoxypropanoic acid, 2-amino-4,4-dimethylbutanoic acid, 2-amino-2-(2,3-epoxycyclohexyl)acetic acid, 2-amino-3-(2,3-epoxycyclohexy)propanoic acid, 2-amino-8-oxo-9,10-epoxydecanoic acid, 2-amino-propanedioic acid, 2-amino-3-methylbutanedioic acid, 2-amino-3,3-dimethylbutanedioic acid, 2-amino4-methylpentanedioic acid, 2-amino-3-methylpentanedioic acid, 2-amino-3-phenylpentanedioic acid, 2-amino-3-hydroxypentanedioic acid, 2-amino-3-carboxypentanedioic acid, 2-amino-4-ethylpentanedioic acid, 2-amino-4-propylpentanedioic acid, 2-amino-4-isoamylpentanedioic acid, 2-amino-4-phenylpentanedioic acid, 2-amino-hexanedioic acid, 2-amino-heptanedioic acid, 2-amino-decanedioic acid, 2-amino-octanedioic acid, 2-

amino-dodecanedioic acid, 2-amino-3-methylenebutanedioic acid, 2-amino-4-methylenepentanedioic acid, 2-amino-3-fluorobutanedioic acid, 2-amino-4-fluoropentanedioic acid, 2-amino-3,3-difluorobutanedioic acid, 2-amino-3-chloropentanedioic acid, 2-amino-3-hydroxybutanedioic acid, 2-amino-4-hydroxypentanedioic acid, 2-amino-4-hydroxyhexanedioic acid, 2-amino-3,4-dihydroxypentanedioic acid, 2-amino-3-(3-hydroxypropyl)butanedioic acid, 2-amino-3-(1-carboxy-4-hydroxy-2-cyclodienyl)propanoic acid, 2-amino-3-(aceto)butanedioic acid, 2-amino-3-cyanobutanedioic acid, 2-amino-3-(2-carboxy-6-oxo-6H-pyranyl)propanoic acid, 2-amino-3-carboxybutanedioic acid, 2-amino-4-carboxypentanedioic acid, 3-amido-2-amino-3-hydroxypropanoic acid, 3-arnido-2-amino-3-methylpropanoic acid, 3-amido-2-amino-3-phenylpropanoic acid, 3-amido-2,3-diaminopropanoic acid, 3-amido-2-amino-3-[N-(4-hydroxyphenyl)amino]propanoic acid, 2,3-diaminopropanoic acid, 2,3-diaminobutanoic acid, 2,4-diaminobutanoic acid, 2,4-diamino-3-methylbutanoic acid, 2,4-diamino-3-phenylbutanoic acid, 2-amino-3-(methylamino)butanoic acid, 2,5-diamino-3-methylpentanoic acid, 2,7-diaminoheptanoic acid, 2,4-diaminoheptanoic acid, 2-amino-2-(2-piperidyl)acetic acid, 2-amino-2-(1-aminocyclohexyl)acetic acid, 2,3-diamino-3-phenylpropanoic acid, 2,3-diamino-3-(4-hydroxyphenyl)propanoic acid, 2,3-diamino-3-(4-methoxyphenyl)propanoic acid, 2,3-diamino-3-[4-(N,N'-dimethyamino)phenyl]propanoic acid, 2,3-diamino-3-(3,4-dimethoxyphenyl)propanoic acid, 2,3-diamino-3-(3,4-methylenedioxyphenyl)propanoic acid, 2,3-diamino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid, 2,3-diamino-3-(2-phenylethyl)propanoic acid, 2,3-diamino-3-propylpropanoic acid, 2,6-diamino-4-hexenoic acid, 2,5-diamino-4-fluoropentanoic acid, 2,6-diamino-5-fluorohexanoic acid, 2,6-diamino-4-hexynoic acid, 2,6-diamino-5,5-difluorohexanoic acid, 2,6-diamino-5,5-dimethylhexanoic acid, 2,5-diamino-3-hydroxypentanoic acid, 2,6-diamino-3-hydroxyhexanoic acid, 2,5-diamino-4-hydroxypentanoic acid, 2,6-diamino-4-hydroxyhexanoic acid, 2,6-diamino-4-

oxohexanoic acid, 2,7-diaminooctanedioic acid, 2,6-diamino-3-carboxyhexanoic acid, 2,5-diamino-4-carboxypentanoic acid, 2-amino-4-(2-(N,N'-diethylamino)ethyl)pentandioic acid, 2-amino-4-(N,N'-diethylamino)pentandioic acid, 2-amino-4-(N-morpholino)pentandioic acid, 2-amino-4-(N,N'-bis(2-chloroethyl)amino)pentandioic acid, 2-amino-4-(N,N'-bis(2-hydroxyethyl)amino)pentandioic acid, 2,3,5-triaminopentanoic acid, 2-amino-3-(N-(2-aminethyl)amino)propanoic acid, 2-amino-3-((2-aminoethyl)seleno)propanoic acid, 2-amino-3-[(2-aminoethyl)thio]propanoic acid, 2-amino4-aminooxybutanoic acid, 2-amino-5-hydroxyaminopentanoic acid, 2-amino-5-[N-(5-nitro-2-pyrimidinyl)amino]pentanoic acid, 2-amino-4-[(7-nitro-2,1,3-benzoxadiazol-4-yl)amino]butanoic acid, 2-amino-3-guanidinopropanoic acid, 2-amino-3-guanidinobutanoic acid, 2-amino-4-guanidobutanoic acid, 2-amino-6-guanidohexanoic acid, 2-amino-6-ureidohexanoic acid, 2-amino-3-(2-iminoimidiazolin-4-yl)propanoic acid, 2-amino-2-(2-iminohexahydropyrimidin-4-yl)acetic acid, 2-amino-3-(2-iminohexahydropyrimidiny-4-yl)propanoic acid, 2-amino4-fluoro-5-guanidopentanoic acid, 2-amino-4-hydroxy-5-guanidopentanoic acid, 2-amino-4-guanidooxybutanoic acid, 2-amino-6-amidinohexanoic acid, 2-amino-5-(N-acetimidoylamino)pentanoic acid, 1-aminocyclopropanecarboxylic acid, 1-amino4-ethylcyclpropanecarboxylic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopentanecarboxylic acid, 1-amino-2,2,5,5-tetramethyl-cyclohexanecarboxylic acid, 1-aminocydoheptanecarboxylic acid, 1-aminocyclononanecarboxylic acid, 2-aminoindan-2-carboxylic acid, 2-aminonorbornane-2-carboxylic acid, 2-amino-3-phenylnorbornane-2-carboxylic acid, 3-aminotetrahydrothiophene-3-carboxylic acid, 1-amino-1,3-cyclohexanedicarboxylic acid, 3-aminopyrrolidine-3-carboxylic acid, 1,4-diaminocyclohexanecarboxylic acid, 6-alkoxy-3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 2- aminobenzobicyclo[2,2,2]octane-2-carboxylic acid,

2-aminoindan-2-carboxylic acid, 1-amino-2-(3,4-dihydroxyphenyl)cyclopropanecarboxylic acid, 5,6-dialkoxy-2-aminoindane-2-carboxylic acid, 4,5-dihydroxy-2-aminoindan-2-caroxylic acid, 5,6-dihydroxy-2-aminotetralin-2-carboxylic acid, 2-amino-2-cyanoacetic acid, 2-amino-3-cyanopropanoic acid, 2-amino-4-cyanobutanoic acid, 2-amino-5-nitropentanoic acid, 2-amino-6-nitrohexanoic acid, 2-amino-4-aminooxybutanoic acid, 2-amino-3-(N-nitrosohydroxyamino)propanoic acid, 2-amino-3-ureidopropanoic acid, 2-amino-4-ureidobutanoic acid, 2-amino-3-phosphopropanoic acid, 2-amino-3-thiophosphopropanoic acid, 2-amino-4-methanephosphonylbutanoic acid, 2-amino-3-(trimethylsilyl)propanoic acid, 2-amino-3-(dimethyl(trimethylsilylmethylsilyl)propanoic acid, 2-amino-2-phenylacetic acid, 2-amino-2-(3-chlorophenyl)acetic acid, 2-amino-2-(4-chlorophenyl)acetic acid, 2-amino-2-(3-fluorophenyl)acetic acid, 2-amino-2-(3-methylphenyl)acetic acid, 2-amino-2-(4ofluorophenyl)acetic acid, 2-amino-2-(4-methylphenyl)acetic acid, 2-amino-2-(4-methoxyphenyl)acetic acid, 2-amino-2-(2-fluorophenyl)acetic acid, 2-amino-2-(2-methylphenyl)acetic acid, 2-amino-2-(4-chloromethylphenyl)acetic acid, 2-amino-2-(4-hydroxymethylphenyl)acetic acid, 2-amino-2-[4-(methylthiomethyl)phenyl]acetic acid, 2-amino-2-(4-bromomethylphenyl)acetic acid, 2-amino-2-(4-(methoxymethy)phenyl)acetic acid, 2-amino-2-(4-((N-benzylamino)methyl)phenyl)acetic acid, 2-amino-2-(4-hydroxylphenyl)acetic acid, 2-amino-2-(3-hydroxylphenyl)acetic acid, 2-amino-2-(3-carboxyphenyl)acetic acid, 2-amino-2-(4-aminophenyl)acetic acid, 2-amino-2-(4-azidophenyl)acetic acid, 2-amino-2-(3-t-butyl-4-hydroxyphenyl)acetic acid, 2-amino-2-(3,5-difluoro-4-hydroxyphenyl)acetic acid, 2-amino-2-(3,5-dihydroxyphenyl)acetic acid, 2-amino-2-(3-carboxy-4-hydroxyphenyl)acetic acid, 2-amino-2-(3,5-di-t-butyl-4-hydroxyphenyl)acetic acid, 2-amino-3-(2-methylphenyl)propanoic acid, 2-amino-3-(4-

ethylphenyl)propanoic acid, 2-amino-3-(4-phenylphenyl)propanoic acid, 2-amino-3-(4-benzylphenyl)propanoic acid, 2-amino-3-(3-fluorophenyl)propanoic acid, 2-amino-3-(4-methylphenyl)propanoic acid, 2-amino-3-(4-fluorophenyl)propanoic acid, 2-amino-3-(4-chlorophenyl)propanoic acid, 2-amino-3-(2-chlorophenyl)propanoic acid, 2-amino-3-(4-bromophenyl)propanoic acid, 2-amino-3-(2-bromophenyl)propanoic acid, 2-amino-3-(3-hydroxyphenyl)propanoic acid, 2-amino-3-(2-hydroxyphenyl)propanoic acid, 2-amino-3-(4-mercaptophenyl)propanoic acid, 2-amino-3-(3-trifluoromethylphenyl)propanoic acid, 2-amino-3-(3-hydroxyphenyl)propanoic acid, 2-amino-3-(4-hydroxyphenyl)propanoic acid, 2-amino-3-[4-(hydroxymethy)phenyl]propanoic acid, 2-amino-3-[3-(hydroxymethyl)phenyl]propanoic acid, 2-amino-3-[3-(aminomethyl)phenyl]propanoic acid, 2-amino-3-(3-carboxyphenyl)propanoic acid, 2-amino-3-(4-nitrophenyl)propanoic acid, 2-amino-3-(4-aminophenyl)propanoic acid, 2-amino-3-(4-azidophenyl)propanoic acid, 2-amino-3-(4-cyanophenyl)propanoic acid, 2-amino-3-(4-acetophenyl)propanoic acid, 2-amino-3-(4-guanidinophenyl)propanoic acid, 2-amino-3-[4-(phenylazo)phenyl]propanoic acid, 2-amino-3-[4-(2-phenylethylenyl)phenyl]propanoic acid, 2-amino-3-(4-trialkylsilylphenyl)propanoic acid, 2-amino-3-(2,4-dimethylphenyl)propanoic acid, 2-amino-3-(2,3-dimethylphenyl)propanoic acid, 2-amino-3-(2,5-dimethylphenyl)propanoic acid, 2-amino-3-(3,5-dimethylphenyl)propanoic acid, 2-amino-3-(2,4,6-trimethylphenyl)propanoic acid, 2-amino-3-(3,4,5-trimethylphenyl)propanoic acid, 2-amino-3-(2,3,4,5,6-pentamethylphenyl)propanoic acid, 2-amino-3-(2,4,-difluorophenyl)propanoic acid, 2-amino-3-(3,4,-difluorophenyl)propanoic acid, 2-amino-3-(2,5,-

difluorophenyl)propanoic acid, 2-amino-3-(2,6,-difluorophenyl)propanoic acid, 2-amino-3-(2,3,5,6-tetrafluorophenyl)propanoic acid, 2-amino-3-(3,5-dichloro-2,4,6-trifluorophenyl)propanoic acid, 2-amino-3-(2,3-difluorophenyl)propanoic acid, 2-amino-3-(2,3-bistrifluoromethylphenyl)propanoic acid, 2-amino-3-(2,4-bistrifluoromethylphenyl)propanoic acid, 2-amino-3-(2-chloro-5-trifluoromethylphenyl)propanoic acid, 2-amino-3-(2,5-difluorophenyl)propanoic acid, 2-amino-3-(2,3,4,5,6-pentafluorophenyl)propanoic acid, 2-amino-3-(2,3-dibromophenyl)propanoic acid, 2-amino-3-(2,5-dibromophenyl)propanoic acid, 2-amino-3-(3,4-dibromophenyl)propanoic acid, 2-amino-3-(3,4,5-triiodophenyl)propanoic acid, 2-amino-3-(2,3-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,6-dihydroxyphenyl)propanoic acid, 2-amino-3-(3-bromo-5-methoxyphenyl)propanoic acid, 2-amino-3-(2,5-dimethoxyphenyl)propanoic acid, 2-amino-3-(2,5-dimethoxy-4-methylphenyl)propanoic acid, 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)propanoic acid, 2-amino-3-(3-carboxy-4-hydroxyphenyl)propanoic acid, 2-amino-3-(3-carboxy-4-aminophenyl)propanoic acid, 2-amino-3-(2-hydroxy-5-nitrophenyl)propanoic acid, 2-amino-3-(2-ethoxy-5-nitrophenyl)propanoic acid, 2-amino-3-(3,4,5-trimethoxyphenyl)propanoic acid, 2-amino-3-(4-azido-2-nitrophenyl)propanoic acid, 2-amino-3-(2-hydroxy-5-nitrophenyl)propanoic acid, 2-amino-3-(2,4-bis-trimethylsilylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-di-t-butylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-benzylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-fluorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-2,3,5,6-tetrafluorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-dichlorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-iodophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-diiodophenyl)propanoic acid, 2-amino-3-(4-hydroxy-2-hydroxyphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-hydroxymethylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-2-

hydroxy-6-methylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-carboxyphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-dinitrophenyl)propanoic acid, substituted thyronines, 2-amino-3-(3,4-dihydroxy-2-chlorophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-bromophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-fluorophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-nitrophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-methylphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-ethylphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-isopropylphenyl)propanoic acid, 2-amino-3-(2-t-butyl-4,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(3-fluoro-4,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(2-fluoro-4,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,5,6-trifluoro-3,4-dihydroxyphenyl)propanolc acid, 2-amino-3-(2,6-dibromo-3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(5,6-dibromo-3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,4,5-trihydroxyphenyl)propanoic acid, 2-amino-3-(2,3,4-trihydroxyphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-5-methoxyphenyl)propanoic acid, 2-amino-3-methyl-3-phenylpropanoic acid, 2-amino-3-ethyl-3-phenylpropanoic acid, 2-amino-3-isopropyl-3-phenylpropanoic acid, 2-amino-3-butyl-3-phenylpropanoic acid, 2-amino-3-benzyl-3-phenylpropanoic acid, 2-amino-3-phenylethyl-3-phenylpropanoic acid, 2-amino-3-(4-chlorophenyl)-3-phenylpropanoic acid, 2-amino-3-(4-methoxyphenyl)-3-phenylpropanoic acid, 2-amino-3,3-diphenylpropanoic acid, 2-amino-3-[4-(N,N- diethylamino)phenyl]heptanoic acid, 2-amino-3-[4-(N,N-diethylamino)phenyl]pentanoic acid, 2-amino-3-(3,4-dimethoxyphenyl)pentanoic acid, 2-amino-3-(3,4-dihydroxyphenyl)pentanoic acid, 2-amino-3-methyl-3-phenylbutanoic acid, 2-amino-3-ethyl-3-phenylpentanoic acid, 2-amino-3-methyl-3-phenylpentanoic acid, 2-amino-3,3-diphenylbutanoic acid, 2-amino-3-fluoro-3-phenylpropanoic acid, 2-amino-3-methylene-3-phenylpropanoic acid, 2-amino-3-methylmercapto-3-phenylpropanoic acid, 2-amino-4-methylmercapto-4-phenylbutanoic acid, 2-amino-4-(3,4-dihydroxyphenyl)butanoic acid, 2-amino-5-(4-

methoxyphenyl)pentanoic acid, 2-amino-4-phenylbutanoic acid, 2-amino-5-phenylpentanoic acid, 2-amino-3,3-dimethyl-5-phenylpentanoic acid, 2-amino-4-phenyl-3-butenoic acid, 2-amino-4-phenoxybutanoic acid, 2-amino-5-phenoxypentanoic acid, 2-amino-2-(indanyl)acetic acid, 2-amino-2-(1-tetralyl)acetic acid, 2-amino-4,4-diphenylbutanoic acid, 2-amino-2-(2-naphthyl)acetic acid, 2-amino-3-(1-naphthyl)propanoic acid, 2-amino-3-(1-naphthyl)pentanoic acid, 2-amino-3-(2-naphthyl)propanoic acid, 2-amino-3-(1-chloro-2-naphthyl)propanoic acid, 2-amino-3-(1-bromo-2-naphthyDpropanoic acid, 2-amino-3-(4-hydroxy-1-naphthyl)propanoic acid, 2-amino-3-(4-methoxy-1-naphthyl)propanoic acid, 2-amino-3-(4-hydroxy-2-chloro-1-naphthyl)propanoic acid, 2-amino-3-(2-chloro-4-methoxy-1-naphthyl)propanoic acid, 2-amino-2-(2-anthryl)acetic acid, 2-amino-3-(9-anthryl)propanoic acid, 2-amino-3-(2-fluorenyl)propanoic acid, 2-amino-3-(4-fluorenyl)propanoic acid, 2-amino-3-(carboranyl)propanoic acid, 3-methylproline, 4-methylproline, 5-methylproline, 4,4-dimethylproline, 4-fluoroproline, 4,4-difluoroproline, 4-bromoproline, 4-chloroproline, 4-aminoproline, 3,4-dehydroproline, 4-methylproline, 4-methyleneproline, 4-mercaptoproline, 4-(4-methoxybenzylmercapto)proline, 4-hydroxymethylproline, 3-hydroxyproline, 3-hydroxy-5-methylproline, 3,4-dihydroxyproline, 3-phenoxyproline, 2-aminoproline, 5-aminoproline, 3-carbamylalkylproline, 4-cyano-5-methyl-5-carboxyproline, 4,5-dicarboxyl-5-methylproline, 2-aziridinecarboxylic acid, 2-azetidinecarboxylic acid, 4-methyl-2-azetidinecarboxylic acid, pipecolic acid, 1,2,3,6-tetrahydropicolinic acid, 3,4-methyleneproline, 2.4-methyleneproline, 4-aminopipecolic acid, 5-hydroxypipecolic acid, 4,5-dihydroxypipecolic acid, 5,6-dihydroxy-2,3-dihydroindole-2-carboxylic acid, 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

1,3-oxazolidine-4-carboxylic acid, 1,2-oxazolidine-3-carboxylic acid, perhydro-1,4-thiazine-3-carboxylic acid, 2,2-dimethylthiazolidine-4-carboxylic acid, perhydro-1,3-thlazine-2-carboxylic acid, selenazolidine4-carboxylic acid, 2-phenylthiazolidine4-carboxylic acid, 2-(4-carboxylicyl)thiazolidine-4-carboxylic acid, 1,2,3,4,4a,9a-hexahydro-beta-carboline-3-carboxylic acid, 2,3,3a,8a-tetrahydropyrrolo(2,3b)indole-2-carboxylic acid, 2-amino-3-(2-pyridyl)propanoic acid, 2-amino-3-(3-pyridyl)propanoic acid, 2-amino-3-(4-pyridyl)propanoic acid, 2-amino-3-(2-bromo-3-pyridyl)propanoic acid, 2-amino-3-(2-bromo-4-pyridyl)propanoic acid, 2-amino-3-(2-bromo-5-pyridyl)propanoic acid, 2-amino-3-(2-bromo-6-pyridyl)propanoic acid, 2-amino-3-(2-chloro-3-pyridyl)propanoic acid, 2-amino-3-(2-chloro-4-pyridyl)propanoic acid, 2-amino-3-(2-chloro-5-pyridyl)propanoic acid, 2-amino-3-(2-chloro-6-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-3-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-4-pyridyl)loropanoic acid, 2-amino-3-(2-fluoro-5-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-6-pyridyl)proloanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-3-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo4-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-5-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-6-pyridyl)propanoic acid, 2-amino-3-(5-hydroxy-2-pyridyl)propanoic acid, 2-amino-3-(5-hydroxy-6-iodo-2-pyridyl)propanoic acid, 2-amino-3-(3-hydroxy-4-oxo-1,4dihydro-1-pyridyl)propanoic acid, N-(5-caroxyl-5-aminopentyl)pyridinium chloride, 1,2,5-trimethyl-4-(2-amino-2-carboxy-1-hydroxyethyl)pyridinium chloride, 2-amino-2-(5-chloro-2-pyridyl)acetic acid, N-(3-amino-3-carboxypropyl)pyridinium chloride, 2-amino-3-(2-pyrryl)propanoic acid, 2-amino-3-(1-pyrryl)propanoic acid, 2-amino-4-(1-pyrryl)butanoic acid, 2-amino-5-(1-pyrryl)pentanoic acid, 2-amino-3-(5-imidazolyl)-3-methylpropanoic acid, 2-amino-3-(5-imidazolyl)-3-ethylpropanoic acid, 2-amino-3-hexyl-3-(5-

imidazolyl)propanoic acid, 2-amino-3-hydroxy-3-(5-imidazolyl)propanoic acid, 2-amino-3-(4-nitro-5-imidazolyl)proloanoic acid, 2-amino-3-(4-methyl-5-imidazolyl)propanoic acid, 2-amino-3-(2-methyl-5-imidazolyl)propanoic acid, 2-amino-3-(4-fluoro-5-imidazolyl)propanoic acid, 2-amino-3-(2-fluoro-5-imidazolyl)propanoic acid, 2-amino-3-(2-amino-5-imidazolyl)propanoic acid, 2-amino-3-(2-phenylaza-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-2-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl4-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-5-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(2-mercapto-5-imidazolyl)propanoic acid, 2-amino-4-(5-imidazolyl)butanoic acid, 2-amino-3-(1-imidazolyl)propanoic acid, 2-amino-3-(2-imidazolyl)propanoic acid, 2-amino-(1-pyrazolyl)propanoic acid, 2-amino-(3-pyrazolyl)propanoic acid, 2-amino-(3,5-dialkyl-4-pyrazolyl)propanoic acid, 2-amino-3-(3-amino-1,2,4-triazol-1-yl)propanoic acid, 2-amino-3-(tetrazol-5-yl)propanoic acid, 2-amino-4-(5-tetrazolyl)butanoic acid, 2-amino-3-(6-methyl-3-indolyl)propanoic acid, 2-amino-3-(4-fluoro-3-indolyl)propanoic acid, 2-amino-3-(5-fluoro-3-indolyl)propanoic acid, 2-amino-3-(6-fluoro-3-indolyl)propanoic acid, 2-amino-3-(4,5,6,7-tetrafluoro-3-indolyl)propanoic acid, 2-amino-3-(5-chloro-3-indolyl)propanoic acid, 2-amino-3-(6-chloro-3-indolyl)propanoic acid, 2-amino-3-(7-chloro-3-indolyl)propanoic acid, 2-amino-3-(5-bromo-3-indolyl)propanoic acid, 2-amino-3-(7-bromo-3-indolyl)propanoic acid, 2-amino-3-(2-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(5-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(7-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(2-alkylmercapto-3-indolyl)propanoic acid, 2-amino-3-(7-amino-3-indolyl)propanoic acid, 2-amino-3-(4-nitro-3-indolyl)propanoic acid, 2-amino-3-(7-nitro-3-indolyl)propanoic acid, 2-amino-3-(4-carboxy-3-indolyl)propanoic acid, 2-amino-3-(3-indolyl)butanoic acid, 2-amino-3-(2,3-dihydro-3-indolyl)propanoic acid, 2-amino-3-

(2,3-dihydro-2-oxo-3-indolyl)propanoic acid, 2-amino-3-alkylmercapto-3-(3-indolyl)propanoic acid, 2-amino-3-(4-aza-3-indolyl)propanoic acid, 2-amino-3-(7-aza-3-indolyl)propanoic acid, 2-amino-3-(7-aza-6-chloro-4-methyl-3-indolyl)propanoic acid, 2-amino-3-(2,3-dihydrobenzofuran-3-yl)propanoic acid, 2-amino-3-(3-methyl-5-7-dialkylbenzofuran-2-yl)propanoic acid, 2-amino-3-(benzothiophen-3-yl)propanoic acid, 2-amino-3-(5-hydroxybenzothiophen-3-yl)propanoic acid, 2-amino-3-eoenzoselenol-3yl)propanoic acid, 2-amino-3-quinolylpropanoic acid, 2-amino-3-(8-hydroxy-5-quinolyl)propanoic acid, 2-amino-2-(5,6,7,8-tetrahydroquinol-5-yl)acetic acid, 2-amino-3-(3-coumarinyl)propanoic acid, 2-amino-2-(benzisoxazol-3-yl)acetic acid, 2-amino-2-(5-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(6-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(7-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(5-bromobenzisoxazol-3-yl)acetic acid, 2-amino-3-(benzimidazol-2-yl)propanoic acid, 2-amino-3-(5,6-dichlorobenzimidazol-2-yl)propanoic acid, 2-amino-3-(5,6-dimethylbenzimidazol-2-yl)propanoic acid, 2-amino-3-(4,5,6,7-hydrobenzirnidazol-2-yl)propanoic acid, 2-amino-2-(benzimidazol-5-yl)acetic acid, 2-amino-2-(1,3-dihydro-2,2-dioxoisobenzothiophen-5-yl)acetic acid, 2-amino-2-(1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl)acetic acid, 2-amino-2-(2-oxobenzimidazol-5-yl)acetic acid, 2-amino-3-(4-hydroxybenzothiazol-6-yl)propanoic acid, 2-amino-3-(benzoxazol-2-yl)propanoic acid, 2-amino-3-(benzothiazol-2-yl)propanoic acid, 2-amino-3-(9-adeninyl)propanoic acid, 2-amino-2-(6-chloro-9-purinyl)acetic acid, 2-amino-2-(6-amino-9-purinyl)acetic acid, 2-amino-3-(6-purinyl)propanoic acid, 2-amino-3-(8-theobrominyl)propanoic acid, 2-amino-2-(1-uracilyl)acetic acid, 2-amino-2-(1-cytosinyl)acetic acid, 2-amino-3-(1-uracilyl)propanoic acid, 2-amino-3-(1-cytosinyl)propanoic acid, 2-amino-4-(1-pyrimidinyl)butanoic acid, 2-amino-4-(4-amino-1-pyrimidinyl)butanoic acid, 2-amino-4-(4-hydroxy-1-pyrimidinyl)butanoic acid, 2-amino-5-(1-pyrimidinyl)pentanoic acid, 2-amino-5-(4-amino-1-

pyrimidinyl)pentanoic acid, 2-amino-5-(4-hydroxy-1-pyrimidinyl)pentanoic acid, 2-amino-3-(5-pyrimidinyl)propanoic acid, 2-amino-3-(6-uracilyl)propanoic acid, 2-amino-3-(2-pyrimidinyl)propanoic acid, 2-amino-3-(6-amino-4-chloro-2-pyrimidinyl)propanoic acid, 2-amino-3-(4-hydroxy-2-pyrimidinyl)propanoic acid, 2-amino-3-(2-amino-4-pyrimidinyl)propanoic acid, 2-amino-3-(4,5-dihydroxypyrimidin-2-yl)propanoic acid, 2-amino-3-(2-thiouracil-6-yl)propanoic acid, 2-amino-2-(5-alkyl-2-tetrahydrofuryl)acetic acid, 2-amino-2-(5-methyl-2,5-dihydro-2-furyl)acetic acid, 2-amino-2-(5-alkyl-2-furyl)acetic acid, 2-amino-2-(2-furyl)acetic acid, 2-amino-2-(3-hydroxy-5-methyl-4-isoxazolyl)acetic acid, 2-amino-3-(4-bromo-3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-3-(4-methyl-3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-3-(3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-2-(3-chloro-D2 -isoxazolin-5-yl)acetic acid, 2-amino-2-(3-oxo-5-isoxazolidinyl)acetic acid, 2-amino-3-(3,5-dioxo-1,2,4-oxadiazolin-2-yl)propanoic acid, 2-amino-3-(3-phenyl-5-isoxazolyl)propanoic acid, 2-amino-3-[3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]propanoic acid, 2-amino-3-(2-thienyl)propanoic acid, 2-amino-2-(2-furyl)acetic acid, 2-amino-2-(2-thienyl)acetic acid, 2-amino-2-(2-thiazolyl)acetic acid, 2-amino-3-(2-thiazolyl)propanoic acid, 2-amino-4-(4-carboxy-2-thiazolyl)butanoic acid, 2-amino-3-(4-thiazolyl)propanoic acid, 2-amino-3-(2-selenolyl)propanoic acid, 2-amino-3-(2-amino-4-selenolyl)propanoic acid, and 2-amino-3-(beta-ribofuranosyl)propanoic acid.

"Amino acids residue" also refers to various amino acids where sidechain functional groups are coupled with appropriate protecting groups known to those skilled in the art. "The Peptides", Vol 3, 3-88 (1981)discloses numerous suitable protecting groups and is incorporated herein by reference for that purpose. Examples of amino acids where sidechain functional groups are coupled with appropriate protecting groups include, but are not limited to, Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu),

Hyp(O^{t}Bu), Thr(O^{t}Bu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), and Thr(OBzl).

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two;

generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit HCV infection or treat the symptoms of HCV

infection in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*, 27-55, occurs when the effect (in this case, inhibition of the desired target) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

SYNTHESIS

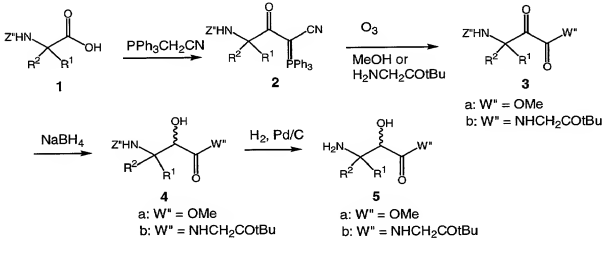
The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is

understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

A series of α-hydroxyesters and α-hydroxyamides of formula **5** are prepared by the method outlined in Scheme 1. Amino acid **1**, wherein Z" is an amino protecting group, is treated with (cyanomethylene)tripheneylphosphorane to give cyano keto phosphorane **2**. Ozonolysis of **2** provides α-ketoester **3a** or α-ketoamide **3b**, which under reduction conditions yields α-hydroxyester **4a** or α-hydroxyamide **4b**. Hydrogenation of **4** in the presence of 10% Pd/C affords α-hydroxyester **5a** or α-hydroxyamide **5b**. (Wasserman, H. H. et al, J. Org. Chem. 1994, 59, 4364).

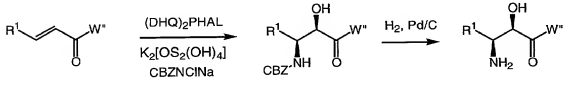
Scheme 1



A series of α-hydroxyl β-amino esters and α-hydroxyl β-amino amides of formula **8** are prepared by the method outlined in Scheme 2. Many of the α,β-unsaturated esters or amides **6** are commercially available or may be easily

prepared from commercially available materials. Sharpless asymmetric aminohydroxylation of α,β-unsaturated ester or amide **6** gives α-hydroxyl β-amino ester or α-hydroxyl β-amino amide **7**. Reductive removal of the carbobenzyloxy (CBZ) group provides **8**. (Sharpless, K. B.; et al, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451. Sharpless, K. B. et al, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2813.)

Scheme 2



6

a: W" = OR
b: W" = NHR

7

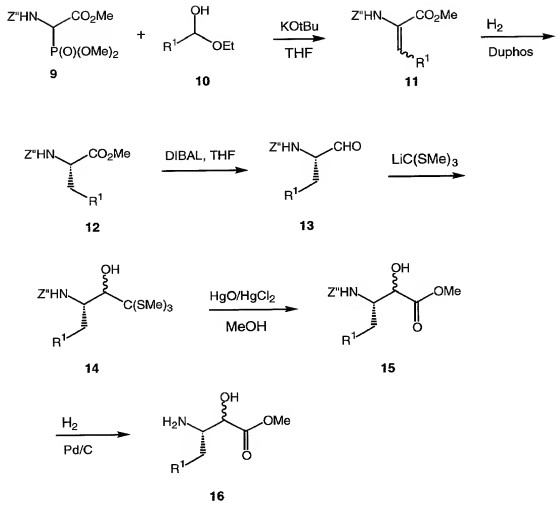
a: W" = OR
b: W" = NHR

8

a: W" = OR
b: W" = NHR

A series of α-hydroxyl β-amino esters of formula **15** are prepared by the method outlined in Scheme 3. Treatment of phosphonoglycine trimethyl ester **9**, wherein Z" is an amino protecting group such as CBZ, with difluoroacetaldehyde hemiacetal **10** in the present of KOtBu yields α,β-unsaturated ester **11**. Hydrogenation of **11** in the present of a chiral Rh catalyst, such as Duphos, selectively reduces the double bond and affords **12** in high enantiomeric excess. DIBAL reduction of methyl ester **12** gives corresponding aldehyde **13**, which under the treatment of lithium tris(methylthhio)methane to provide α-hydroxyl compound **14**. Finally, α-hydroxyl β-amino ester of formula **15** is obtained when **14** is treated with Hg^{2+}. (Kaneko, S. K.; et al, *J. Org. Chem.* **1993**, *58*, 2302.)

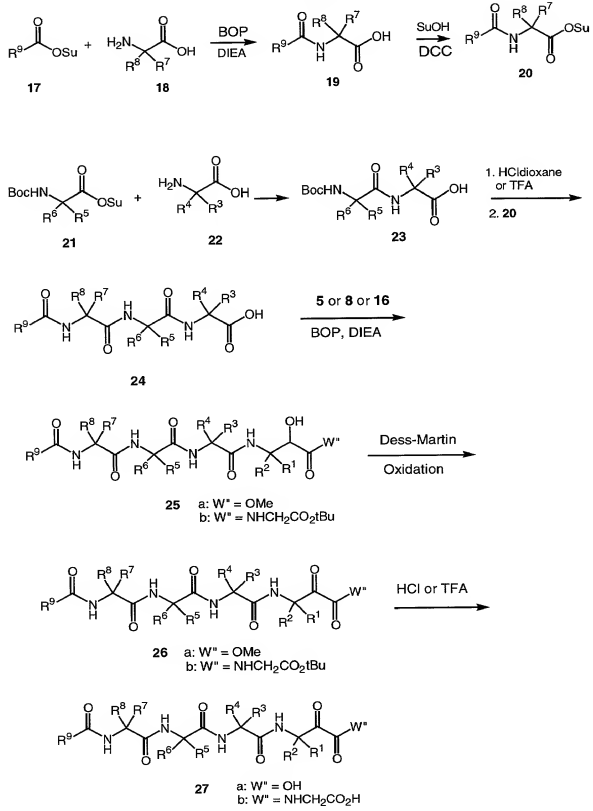
Scheme 3



A series of α-ketoamides or acids of formula **27** are prepared by the method outlined in Scheme 4. Amino acid **18** is coupled with **17** under regular coupling conditions to afford **19**, which is then converted to its succinimide **20**. Compound **20** is coupled with dipeptide **23**, which is prepared by the same method, to yield tripeptide **24**. Compound **24** is reacted with the α-hydroxyl β-amino ester or amide under standard coupling conditions to give α-hydroxyl ester or amide **25**. Dess-Martin oxidation converts **25** to α-keto ester or amide **26**. The methyl ester **26** is either saponified to provide α-keto acid **27a**, or deprotected in

TFA to afford α-keto amide **27b**. (Angelastro,, M. R. *J. Med. Chem.* **1990**, *33*, 13.)

Scheme 4



17 **18** **19** **20** **21** **22** **23** **24**

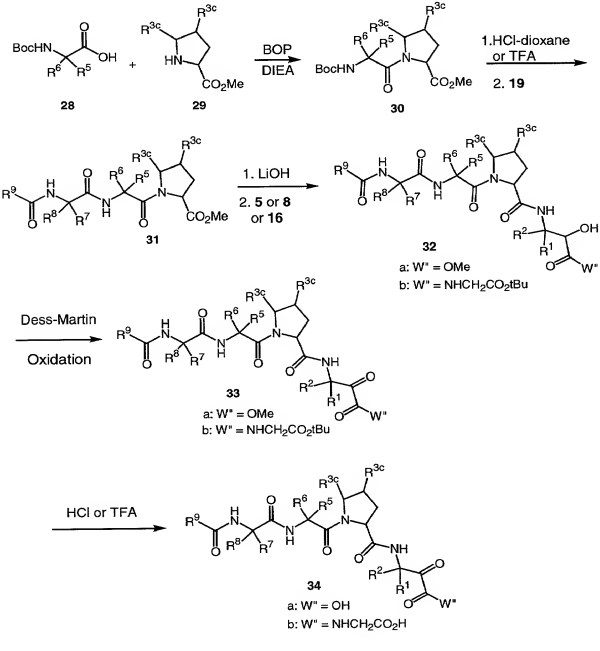
25 a: W" = OMe
b: W" = $NHCH_2CO_2tBu$

26 a: W" = OMe
b: W" = $NHCH_2CO_2tBu$

27 a: W" = OH
b: W" = $NHCH_2CO_2H$

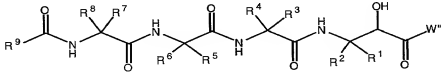
A series of α-keto amides or acids of formula **34** are prepared by the method outlined in Scheme 5. Coupling of acid **28** with proline derivative **29** in the present of BOP and DIEA yields compound **30**. Deprotection of BOC group in **30** followed by the coupling with the same intermediate **19** provides compound **31**. Application of similar chemistry to that described in Scheme 4 leads to the synthesis of α-keto amides or acids of formula **34**.

Scheme 5



A series of α-ketoamides of formula **36** are prepared by the method outlined in Scheme 6. From the same intermediate **25a**, saponification affords the corresponding acid, which reacts with amines of formula **37** to give α-hydroxyamide **35**. Dess-Martin oxidation of **35** provides α-ketoamide **36**.

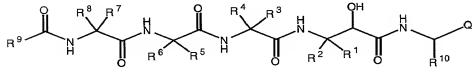
Scheme 6



25a

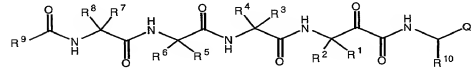
1. LiOH
2. NH_2CH_2Q

37



35

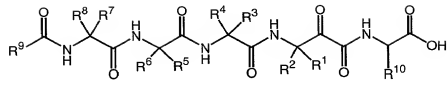
Dess-Martin Oxidation



36

A series of α-ketoamides of formula **38** are prepared by the method outlined in Scheme 7. Treatment of intermediate **27b** with sulfonamide of type **39** in the presence of a coupling agent such as EDCI and DMAP provides α-ketoamide **38**. (Andery, R. H.; J. Org. Chem. 1986, 987).

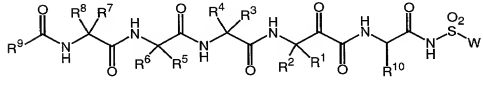
Scheme 7



27b

NH_2SO_2W

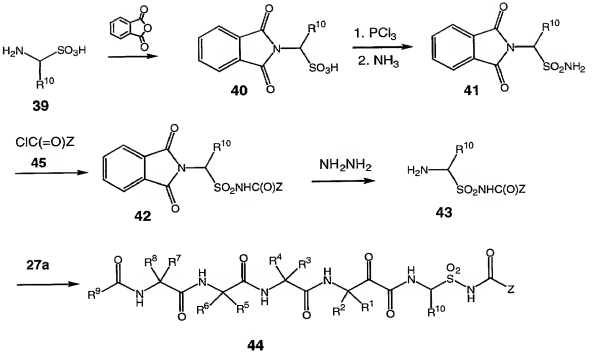
39



38

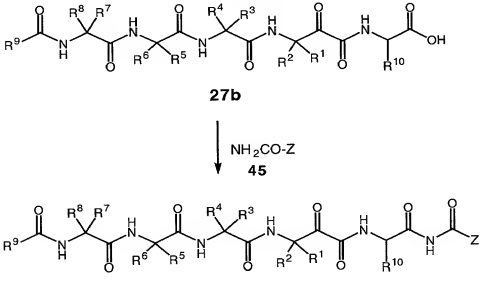
A series of α-ketoamides of formula **44** are prepared by the method outlined in Scheme 8. Protection of the amino group in **39** gives sulfonic acid **40**. Treatment of compound **40** with PCl_3 followed by ammonia yields sulfonamide **41**. Acylation of **41** with an acid chloride of type **45** affords acyl sulfonamide **42**. Deprotection of the N terminal **42** with hydrazine gives amine **43**. Coupling of amine **43** with α-ketoacid **27a** provides α-ketoamide **44**.

Scheme 8



A series of α-ketoamides of formula **46** are prepared by the method outlined in Scheme 9. Treatment of intermediate **27b** with amide of type **45** in the present of DCC and DMAP provides α-ketoamide **46**. (Almeida, P. S. et al. *Tetrahedron Lett.* **1991**, *23*, 2671).

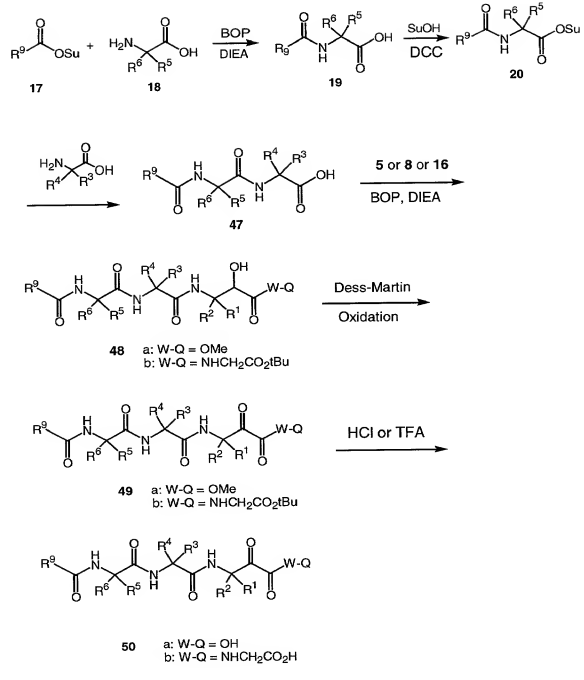
Scheme 9



A series of α-ketoamides of formula **50** are prepared by a similar method to the preparation of compound **27** as outlined in Scheme 10.

Many of the CBZ protected amino acids and amino acid methyl esters are commercially available or may be prepared from commercial amino acid derivatives by simple protecting group manipulations. Others may be synthesized in racemic form using the Strecker synthesis or amidomalonate synthesis. In addition, the Myers pseudoephedrine glycinamide alkylation method (Myers, A. G.; Gleason, J. L.; Yoon, T; Kung, D. W.. *J. Am. Chem. Soc.* **1997**, *119*, 656-673) and the Evans electrophilic azidation (Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011) may be used to prepare unnatural amino acids in enantiomerically pure form.

Scheme 10



17 18 19 20

47

48 a: W-Q = OMe
b: W-Q = $NHCH_2CO_2tBu$

49 a: W-Q = OMe
b: W-Q = $NHCH_2CO_2tBu$

50 a: W-Q = OH
b: W-Q = $NHCH_2CO_2H$

When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotheraphy* **1995**, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tet. lett.* **1995**, *36*, 8937-8940).

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

Examples

Abbreviations used in the examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "rt" for room temperature, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "MS" for mass spectrometry, "NMR" for nuclear magnetic resonance spectroscopy, "^{1}H" for proton, "HPLC" for high pressure liquid chromatography, "tlc" for thin layer chromatography, "v/v" for volume to volume ratio, "atm" for atmosphere, "α", "β", "R", and "S" are stereochemical designations familiar to one skilled in the art.

Abbreviations used in the specification are defined as follows:

"BOP" is benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate;

"Bzl" or "Bn" is benzyl;

"CBZ" is carbobenzyloxy;

"COD" is cyclooctadiene;

"DCC" is 1,3-dicyclohexylcarbodiimide;

"$(DHQ)_2$PHAL" is hydroquinine 1,4-phthalazinediyl diether;

"DIBAL" is diisobutylaluminum hydride;

"DIEA" is Diisopropylethylamine;

"DMAP" is 4-dimethylamino pyridine;

"DMF" is dimethylformamide ;

"DMSO" is dimethylsyulfoxide;

"Duphos" is (+)-1,2-bis(2S,5S)-2,5-diethylphospholano)-

benzene(cyclooctadiene)rhodium(I) trifluoromethanesulfonate

"EtOAc" is ethylacetate;

"EDCI" is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

"Pz" is pyrazinyl;

"SuOH" is N-hydroxysuccinimide; and

"TFA" is trifluoroacetic acid.

Example A1

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoylglycine

Step (A1a): At 0°C, DIEA (12.1Ml, 69.5 mmol) was added to the suspension of Ph_3PCH_2CNCl in CH_2Cl_2. The suspension turned to clear. The aminobutyric acid (15.0g, 63.2 mmol) was added followed by addition of EDCI (12.7g, 66.4 mmol) and DMAP (0.77g, 6.32 mmol). The resulted mixture was stirred at 0°C for 2h and at rt over night. Most of the solvent was evaporated and the residue was chromatographed on silica gel (50-60% EtOAc:Hexane). The product (Scheme 1, **2**) was obtained as a white solid 22.7g in 69% yield. MS found $(M+1)^+$ 521.3

Step (A1b): The ylide obtained from Step(A1a) (10g, 19.2 mmol) was dissolved in CH_2Cl_2 (200 mL) and the mixture was cooled to -78°C. To this mixture at -78°C was purged O_3 until the color changed to blue. Excess O_3 was removed by purging N_2 into the mixture. The solution of Gly-OtBu hydrochloride (3.54g, 21.1 mmol), pretreated with DIEA and precooled) in CH_2Cl_2 was added at -78°C to the above reaction mixture and stirred at -78°C for 30 min, then warmed to rt. Solvent was evaporated and the residue was chromatographed on silica gel (20-50% EtOAc:hexane). The α-ketoamide (Scheme 1, **3**) was obtained in 58% yield as an oil (4.25g). MS found $(M+Na)^+$ 401.1. Similarly, the

reaction mixture can be quenched with methanol instead of Gly-OtBu to provide the corresponding α-ketoester (Scheme 1, **3a**).

Step (A1c): To a solution of ketoamide obtained from Step (A1b) (0.23g, 0.61 mmol) in THF (10 mL) at 0°C was added sodium borohydride (42mg, 1.22mmol) in portions. After stirring at 0°C for 30 min, the reaction mixture was quenched with acetone. Most of the solvent was evaporated and the residue was dissolved in EtOAc, washed with H_2O and brine. Chromatography on silica gel (40% EtOAc in hexane) yielded 124 mg α-hydroxyamide (Scheme 1, **4**) as a colorless oil (53%). MS found $(M+1)^+$ 381.2.

Step (A1d): The α-hydroxyamide obtained from Step (A1c) (124 mg, 0.326 mmol) was dissolved in MeOH (50 mL) and Pd/C 10mg) was added. The mixture was hydrogenated under 1 atm. for 40 min. The reaction mixture was filtered and concentrated. The amine (Scheme 1, **5**) was obtained in 99% yield as a white solid 82 mg. MS found $(M+1)^+$ 247.3. Similarly, the α-ketoester from (A1b) was converted to α-hydroxyester (Scheme 1, **5a**) via step (A1c).

Step (A1e): DCC (3.99g, 19.3 mmol, 1.2 eq) was added to a solution of 2-pyrazine carboxylic acid (2.0g, 16.1 mmol) and N-hydroxysuccinimide (1.95g, 16.9 mmol, 1.05eq) in 100mL THF at 0°C. The mixture was stirred at rt over night. The reaction mixture was filtered, concentrated and dried. The product was obtained in 91% yield as a solid (Scheme 4, **17**).

Step (A1f): At 0°C under N_2, DIEA (13.3mL, 76.13 mmol) was added to a solution of material from Step (A1e) (10g, 45.2 mmol) and leucine (5.93g, 45.3 mmol) in 120 mL DMF. After addition, the resulted mixture was stirred at rt over night. The mixture was diluted with 200 mL of EtOAc,

washed with 1N HCl (2x30 mL), H_2O (2x50 mL) and brine, and dried over $MgSO_4$. The solvent was removed and dried on vacuum to provide a white solid as pure product (95%) (Scheme 4, **19**). MS found $(M-1)^-$ 219.

Step (A1g): Following a procedure analogous to Step (A1e), the material from Step (A1f) (1.0g, 4.5 mmol) was treated with N-hydroxysuccinimide (530 mg, 4.5 mmol), providing the desired product as a white solid (1.28g, 90%)(Scheme 4, **20**).

Step (A1h): Following a procedure analogous to Step (A1f), the succinimide ester of N-Boc isoleucine (10g, 30.45 mmol) was treated with cyclohexylalanine (6.32g, 30.45 mmol) in the presence of DIEA in DMF, providing the desired product (Scheme 4, **23**) as a white solid (95%). MS found $(M+1)^+$ 385.3.

Step (A1i): The material from Step (A1h) (1.0g, 2.6 mmol) was treated with 4M HCl in dioxane for 2h at rt. Solvent was evaporated and the residue was dried. Following a procedure analogous to Step (A1f), the material from above was treated with the material from Step (A1g) (0.83g, 2.6 mmol) in the presence of DIEA in DMF, providing the desired product (Scheme 4, **24**) as a white solid (1.16g, 89%). MS found $(M+1)^+$ 504.3.

Step (A1j): To a solution of the above material from Step (A1i) (1g, 1.99 mmol) in 100mL of DMF at 0°C was added BOP (1.3g, 2.98 mmol) and DIEA (0.52 mL, 2.98 mmol). The mixture was stirred at this temp. for 20 min. Then a solution of the material from Step (A1d) (490 mg, 1.99 mmol) in 10 mL of DMF was added to the above mixture followed by addition of another portion of DIEA (0.52 mL, 1.99 mmol). The resulting mixture was stirred at 0°C for 1h and rt overnight. The reaction mixture was diluted with EtOAc (400 mL), washed with 1N HCl, saturated $NaHCO_3$, H_2O,

brine, dried and concentrated. Chromatography on silica gel (70% EtOAc in hexane) provided desired product (1.22g, 84%) as a white solid (Scheme 4, **25b**). MS found $(M+1)^+$ 732.4.

Step (A1k): To a mixture of the above material from Step (A1j) (200 mg, 0.27 mmol) and molecular sieves in 6 mL of CH_2Cl_2 was added Dess-Martin reagent (172 mg, 0.41 mmol). The resulting mixture was stirred at rt for 2h. Then the mixture was filtered and the residue was chromatographed on silica gel (5% MeOH in $CHCl_3$) to provide the desired ketoamide (Scheme 4, **26b**) as a white solid (169mg, 86%). MS found $(M+1)^+$ 730.3.

Step (A1l): A solution of the above material from Step (A1k) (300 mg, 0.41 mmol) in CH_2Cl_2 was treated with TFA (20 mL, 1:1) and the mixture was stirred at rt for 2h. After evaporation of the solvent, the residue was dried in vacuum and the title ketoamide (Scheme 4, **27b**), Example 1A, was obtained (273 mg, 99%) as a light yellow solid. MS found $(M+1)^+$ 674.4.

Example A2

(3S)-2-oxo-3-{[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino}-N-(2H-tetrazol-5-ylmethyl) pentanamide

Step (A2a): The ylide obtained from Step (A1a) (10g, 19.2 mmol) was dissolved in CH_2Cl_2 (200 mL) and the mixture was cooled to -78°C. To this mixture was purged O_3 at this temp. until the color of the mixture changed to blue. Excess O_3 was removed by purging N_2 into the mixture. Methanol was added at -78°C to the above reaction mixture. The resulting mixture was stirred at -78°C for 30 min and warmed to rt. Solvent was evaporated and the residue was chromatographed on silica gel (20-50% EtOAc:hexane). The

α-ketoester (Scheme 1, **3a**) was obtained in 87% yield as a white solid. MS found $(M+Na)^+$ 280.4.

Step (A2b): Following a procedure analogous to Step (A1c), the ketoester from Step (A2a) (1g, 3.6 mmol) was reduced with $NaBH_4$ to the desired α-hydroxyester (Scheme 1, **4a**) as a white solid (0.86g, 86%). MS found $(M+1)^+$ 282.3.

Step (A2c): Following a procedure analogous to Step (A1d), the α-hydroxyester (0.7g, 2.5 mmol) from Step (A2b) above was hydrogenated in the present of 10% Pd/C to give the desired amine (Scheme 1, **5a**) as a white solid (3.6g, >95%). MS found $(M+1)^+$ 148.3.

Step (A2d): Following a procedure analogous to Step (A1j), the material from Step (A2c) above (0.5g, 3.4 mmol) was coupled with the material from Step (A1i) (1.7g, 3.4 mmol) to provide the desired the α-hydroxyester (Scheme 4, **25a**) as a white solid (1.4g, 67%). MS found $(M+1)^+$ 633.3.

Step (A2e): To a solution of the above material from Step (A2d) (500 mg, 0.79 mmol) in 8 mL THF at 0°C was added 8mL of 1N LiOH solution. After stirring at this temp for 3h, the mixture was acidified with 1N HCl to pH 5. Solvent was evaporated and the residue was extrated with EtOAc (3x50 mL). The combined organic portion was washed with water, brine and dried. Removal of solvent yielded the acid product (463mg, 95%) as white solid. MS found $(M+1)^+$ 619.2, $(M-1)^-$ 617.1.

Step (A2f): Aminomethyltetrazole (75 mg, 0.76 mmol) was suspended in 6 mL mixed solvent of DMF/DMSO (1:1). To this mixture was added DIEA (0.3 mL), material from Step (A2e) above (50 mg, 0.081 mmol) and BOP reagent (200 mg). The resulting mixture was stirred at rt for 3h. Then the mixture was HPLC purified (grandient starting from 30%

water in acetonitrile) to give the desired product as a white solid (46mg, 82%). MS found $(M+1)^+$ 701.4.

Step (A2g): The material from Step (A2f) above (46 mg, 0.066 mmol) was dissolved in 5.0 mL methylenechloride. Dess-Martin reagent (100 mg) was added. The mixture was stirred at rt for 1.5h. Then the reaction mixture was filtered and solvent was removed. HPLC purification (grandient starting from 30% water in acetonitrile) gave Example A2, a white solid, as pure product (40mg, 89%). MS found $(M+1)^+$ 698.4.

Example A3

2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl]amino]-N-(sulfomethyl)pentanamide

Step (A3a): Following a procedure analogous to Step (A2f), the material from Step (A2e) (50 mg, 0.081 mmol) was coupled with aminomethanesulfonic acid (18 mg, 0.16 mmol), providing the title product as a light-yellow solid (44mg, 76%). MS found $(M+1)^+$ 712.3.

Step (A3b): Following a procedure analogous to Step (A2g), the above material from Step (3a) (44mg, 0.062 mmol) was oxidized with Dess-Martin reagent to give the title α-ketoamide (30mg, 68%). MS found $(M+1)^+$ 710.3.

Example A4

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(2-nitrophenyl)sulfonyl]glycinamide

Step (A4a): To the mixture of the material from Step (A11) (Scheme 4, **27b**) (34 mg, 0.05 mmol) in CH_2Cl_2 (5mL) at 0°C were added a solution of (2-nitrophenyl)sulfonamide (15 mg, 0.075 mmol) and DMAP (6mg, 0.05mmol) in CH_2Cl_2, followed by addition of EDCI (14.3 mg, 0.075 mmol). The resulting

mixture was stirred at rt for 40 min. The reaction mixture was diluted with EtOAc, washed with H_2O, brine, dried and concentrated. HPLC purification gave the title product as a white solid. MS found $(M+1)^+$ 858.3.

Example A5

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(methylsulfonyl) glycinamide

Step (A5a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with methylsulfonamide to provide the title compound. MS found $(M+1)^+$ 751.4.

Example A6

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(phenylmethyl) sulfonyl]glycinamide

Step (A6a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with phenylmethyl-sulfonamide to provide the title compound. MS found $(M+1)^+$ 825.4.

Example A7

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(phenylsulfonyl) glycinamide

Step (A7a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with phenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 813.4.

Example A8

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(trifluoromethyl)sulfonyl]glycinamide

Step (A8a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with trifluoromethylsulfonamide to provide the title compound. MS found $(M+1)^+$ 805.4.

Example A9

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-nitrophenyl)sulfonyl]glycinamide

Step (A9a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (2-nitrophenyl)sulfonamide to provide the title compound. MS found $(M+1)^+$ 858.1.

Example A10

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-nitrophenyl)sulfonyl]glycinamide

Step (A10a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (4-nitrophenyl)sulfonamide to provide the title compound. MS found $(M+1)^+$ 858.3.

Example A11

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-fluorophenyl)sulfonyl]glycinamide

Step (A11a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (4-fluorophenyl)sulfonamide to provide the title compound. MS found $(M+1)^+$ 831.4.

Example A12

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-fluorophenyl)sulfonyl]glycinamide

Step (A12a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (3-fluorophenyl)sulfonamide to provide the title compound. MS found $(M+1)^+$ 831.4.

Example A13

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-fluorophenyl) sulfonyl]glycinamide

Step (A13a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (2-fluorophenyl)sulfonamide to provide the title compound. MS found $(M+1)^+$ 831.5.

Example A14

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chlorophenyl) sulfonyl]glycinamide

Step (A14a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (4-chlorophenyl)sulfonamide to provide the title compound. MS found $(M+1)^+$ 848.3.

Example A15

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentano yl-N-[(3-chlorophenyl) sulfonyl]glycinamide

Step (A15a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (3-

chlorophenyl)sulfonamide to provide the title compound. MS found $(M+1)^+$ 848.4.

Example A16

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-(thionitroso) phenyl]sulfonyl]glycinamide

Step (A16a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-(thionitroso)phenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 870.6.

Example A17

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]glycinamide

Step (A17a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-[(trifluoromethyl)sulfonyl]phenyl-sulfonamide to provide the title compound. MS found $(M+1)^+$ 946.1.

Example A18

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-(trifluoromethyl)phenyl]sulfonyl]glycinamide

Step (A18a) Following a procedure analogous to (4a), compound **27b** (Scheme 4) was coupled with 4-(trifluoromethyl)-phenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 881.8.

Example A19

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-cyanophenyl)sulfonyl]glycinamide

Step (A19a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-cyanophenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 839.0.

Example A20

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3-chloro-4-methylphenyl)sulfonyl]glycinamide

Step (A20a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-chloro-4-methylphenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 862.3.

Example A21

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chloro-3-nitrophenyl)sulfonyl]glycinamide

Step (A21a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-chloro-3-nitrophenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 893.4.

Example A22

N-(2-pyrazinylcarbonyl)-L-leucyl-L- isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichlorophenyl)sulfonyl]glycinamide

Step (A22a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3,5-dichlorophenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 882.9.

Example A23

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-methyl-3-nitrophenyl)sulfonyl]glycinamide

Step (A23a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-methyl-3-nitrophenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 873.1.

Example A24

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-(trifluoromethyl)phenyl]sulfonyl]glycinamide

Step (A24a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-5-(trifluoromethyl)phenyl-sulfonamide to provide the title compound. MS found $(M+1)^+$ 916.5.

Example A25

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide

Step (A25a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-carboxy-2-chlorophenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 892.3.

Example A26

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2,5-dichlorophenyl)sulfonyl]glycinamide

Step (A26a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2,5-

dichlorophenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 879.5.

Example A27

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,4-difluorophenyl)sulfonyl]glycinamide

Step (A27a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3,4-diflorophenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 849.6.

Example A28

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]glycinamide

Step (A28a) Following a procedure analogous to Step (A4a), compound 27b (Scheme 4) was coupled with 3,5-dichoro-2-hydroxyphenylsulfonamide to provide the title compound. MS found $(M-1)^-$ 895.5.

Example A29

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[(2,4,5-trichlorophenyl)-sulfonyl]glycinamide

Step (A29a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2,4,5-trichlorophenylsulfonamide to provide the title compound. MS found $(M-1)^-$ 913.3.

Example A30

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(5-carboxy-4-chloro-2-fluorophenyl)sulfonyl]glycinamide

Step (A30a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-carboxy-4-chloro-2-fluorophenyl sulfonamide to provide the title compound. MS found $(M+1)^+$ 910.6.

Example A31

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]glycinamide

Step (A31a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-(dimethylamino)-1-naphthalenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 907.3.

Example A32

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(2-naphthalenylsulfonyl)glycinamide

Step (A32a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-naphthalenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 864.2.

Example A33

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L- alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[(4-(phenyl)phenyl)-sulfonyl]glycinamide

Step (A33a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-biphenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 889.5.

Example A34

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(6-ethoxy-2-benzothiazolyl)sulfonyl]glycinamide

Step (A34a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (6-ethoxy-2-benzothiazolyl)sulfonamide to provide the title compound. MS found $(M+1)^+$ 915.2.

Example A35

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-[[(phenylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

Step (A35a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-5-[[(phenylmethyl)amino]carbonyl]-phenyl sulfonamide to provide the title compound. MS found $(M+1)^+$ 980.6.

Example A36

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[[(2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

Step (A36a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with [[(2-trifluoroethyl)amino]carbonyl]phenyl sulfonamide to provide the title compound. MS found $(M-1)^-$ 970.5.

Example A37

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L- alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[[(cyclopropylmethyl)amino]carbonyl]phenyl]sulfonyl] glycinamide

Step (A37a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-5-[[(cyclopropylmethyl)amino]-carbonyl]phenyl] sulfonamide to provide the title compound. MS found $(M+1)^+$ 944.4.

Example A38

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-nitro-4-(2-pyrimidinylthio)phenyl]sulfonyl]glycinamide

Step (A38a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-nitro-4-(2-pyrimidinylthio)phenyl sulfonamide to provide the title compound. MS found $(M+1)^+$ 968.4.

Example A39

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-4-(acetylamino)phenyl]sulfonyl]glycinamide

Step (A39a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-4-(acetylamino)phenyl sulfonamide to provide the title compound. MS found $(M-1)^-$ 902.5.

Example A40

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-chloro-4-(2-benzoxazolylthio)phenyl]sulfonyl]glycinamide

Step (A40a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-chloro-4-(2-benzoxazolylthio)phenyl sulfonamide to provide the title compound. MS found $(M-1)^-$ 1005.5.

Example A41

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[3,5-dichloro-4-(4-nitrophenoxy)phenyl]sulfonyl]glycinamide

Step (A41a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3,5-dichloro-4-(4-nitrophenoxy)phenyl sulfonamide to provide the title compound. MS found $(M+1)^+$ 1018.5.

Example A42

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]glycinamide

Step (A42a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-(acetylamino)-1,3,4-thiadiazol-2-yl sulfonamide to provide the title compound. MS found $(M+1)^+$ 878.5.

Example A43

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-cyanophenyl)sulfonyl]glycinamide

Step (A43a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-cyanophenylsulfonamide to provide the title compound. MS found $(M+1)^+$ 838.4.

Example A44

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[3-(aminosulfonyl)-5-chlorophenyl]sulfonyl]glycinamide

Step (A44a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-(aminosulfonyl)-

5-chlorophenyl sulfonamide to provide the title compound. MS found $(M-1)^-$ 924.4.

Example A45

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[[3,5-bis(trifluoromethyl)phenyl]sulfonyl]glycinamide

Step (A45a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3,5-bis(trifluoromethyl)phenyl sulfonamide to provide the title compound. MS found $(M+1)^+$ 949.4.

Example A46

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[4-[5-[3-(4-chlorophenyl)-3-oxo-1-propenyl]-2-furanyl]phenyl]sulfonyl]glycinamide

Step (A46a): Following a procedure analogous to step (A4a), compound **27b** (Scheme 4) was coupled with 4-[5-[3-(4-chlorophenyl)-3-oxo-1-propenyl]-2-furanyl]phenyl sulfonamide providing the title compound. MS found $(M+1)^+$ 1043.5.

Example A47

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[[(phenylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

Step (A47a): Following a procedure analogous to step (A4a), **27b** (Scheme 4) was coupled with 3-[(phenylmethyl)amino]-carbonyl]phenyl]sulfonamide providing the title product as crystalline solid. MS found $(M+1)^+$ 946.6.

Example A48

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[[(2,2,2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

Step (A48a): Following a procedure analogous to step (A4a), **27b** (Scheme 4) was coupled with 3-[[(2,2,2-trifluoroethyl)amino]carbonyl]phenyl]sulfonamide providing the title product as crystalline solid. MS found $(M+1)^+$ 938.5.

Example A49

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[(benzoylamino)sulfonyl]-5-chlorophenyl]sulfonyl]glycinamide

Step (A49a): Following a procedure analogous to step (A4a), **27b** (Scheme 4) was coupled with 3-[(benzoylamino)sulfonyl]-5-chlorophenyl]-sulfonamide providing the title product as crystalline solid. MS found $(M+1)^+$ 1030.6.

Example A50

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine

Step (A50a): To a suspension of KO*t*Bu (3.55g, 31.7mmol) in 15mL CH_2Cl_2 was added N-CBZ-phosphonolycine trimethyl ester (9.46g, 28.5mmol) at -78°C under N_2. This mixture was stirred for 15min at this temperature and 2,2-difluoroacetaldehyde ethyl hemiacetal (4.0g, 31.7mmol) was added slowly. The resulted mixture was warmed up to room temperature and stirred overnight. Most solvent was removed and the residue was dissolved in ethyl acetate. The mixture was washed with cold water, dried over magnesium sulfate and concentrated. Flash chromatography (10-15% EtOAc/Hexane) gave the desired alkene (1.97g, 24%) (Scheme

3, **11**) as a clear oil (4:1 mixture of Z:E isomers). $(M+1)^+$ 286.3.

Step (A50b): A mixture the material from Step (A50a) (0.90g, 3.16mmol) and of (+)-1,2-bis((2S,5S)-2,5-diethyl-phospholano)benzene-(cyclooctadiene)rhodium(I) trifluoromethanesulfonate ([Rh(COD)(S,S-di-Ethyl-DUPHOS)]$^+CF_3SO_3^-$) (25mg, 0.03mmol, 1 mol%) in 20mL MeOH was hydrogenated at 50psi for 15h. After evaporation of solvent, the residue was dissolved in 30% EtOAc/Hexane and the solution was passed through a pad of silica gel to remove trace amount of the catalyst. Evaporation of solvent yielded the desired compound (Scheme 3, **12**) as a crystalline solid (0.91g, 100%).

Step (A50c): To a solution of the material from Step (A50b) (1.95g, 5.23mmol) in 50mL CH_2Cl_2 under N_2 was added dropwise 5.49mL DIBAL (1.0M solution in CH_2Cl_2, 5.49mmol) at -78°C over 15min. After stirring at this temperature for 2h, the mixture was quenched with 10mL 5% potassium hydrogen sulfate solution. Then the mixture was warmed up to room temperature, diluted with CH_2Cl_2, washed with $KHSO_4$, $NaHCO_3$ and brine, dried over $NaSO_4$ and concentrated. Flash chromatography (15-30% EtOAc/Hexane) afforded 1.20g (89%) of the desired aldehyde (Scheme 3, **13**) as a white solid.

Step (A50d): Butyl lithium (2.5M solution in hexane, 4.1mL, 10.3mmol) was added dropwise to a solution of tris(methylthio)methane (1.58g, 10.3mmol) in 20mL THF at -64°C and the mixture was stirred at this temperature for 20min. Then a solution of 0.66g (2.57mmol) of the material from Step (A50c)in 5.0mL THF was added dropwise to the above mixture over 10min. The resulting mixture was stirred at -30°C and warmed up to room temperature. Then the reaction mixture was quenched with saturated NH_4Cl, and diluted with ethyl acetate. The organic phase was

separated and washed with 5% $KHSO_4$, H_2O, $NaHCO_3$, brine, dried over $NaSO_4$ and concentrated. Flash chromatography (10-15% EtOAc/Hexane) yielded 0.90g (85%) of the desired product (Scheme 3, **14**) as a clear oil (a mixture of two diasteromers).

Step (A50e): To a solution of 0.15g (0.36mmol) of the material from Step (A50d) in a mixed solvent of MeOH/H_2O (12mL/1.0mL) were added 0.46g (1.69mmol) mercury(II) chloride and 0.12g (0.58mmol) mercury(II) oxide. The resulted suspension was stirred at room temperature for 2h. Then the reaction mixture was filtered through a pad of Celite and most of the solvent was removed. The residue was dissolved in ethyl acetate, and this mixture was washed with 70% ammonium acetate, saturated ammonium chloride, sodium bicarbonate and dilute NaCl solution, dried over magnesium sulfate and concentrated. Chromatography (30% EtOAc/Hexane) gave 0.11g (96%) of the desired product (Scheme 3, **15**) as a clear oil (a mixture of two diasteromers).

Step (A50f): Following a procedure analogous to Step (A1d), the material from Step (A50e) was hydrogenated to afford the desired α-hydroxyl β-amino ester (Scheme 3, **16**) as a crystalline solid.

Step (A50g): Following a procedure analogous to Step (A1j), the material from Step (A50f) was coupled with compound **24** (Scheme 4) to give the α-hydroxyester (Scheme 4, **25a**) as a crystalline solid.

Step (A50h): Following a procedure analogous to Step (A2e), the material from Step (A50g) was converted to the desired α-hydroxyacid.

Step (A50i): Following a procedure analogous to Step (A1i), the above acid from Step (A50h) was coupled with

Gly-OtBu to afford the desired product (Scheme 4, **25b**) as a crystalline solid.

Step (A50j): Following a procedure analogous to Step (A1k), the material from Step (A50i) was oxidized to α-ketoamide (Scheme 4, **26b**) as crystalline solid.

Step (A50k): Following a procedure analogous to Step (A1l), the material from Step (A50j) was treated with TFA to afford the title compound (Scheme 4, **27b**) as a white solid. MS found $(M+1)^+$ 710.4.

Example A51

(3S)-5,5-difluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)- L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N- (2H-tetrazol-5-ylmethyl)pentanamide

Step (A51a): Following a procedure analogous to Steps (A1f) and (A1g), the material from Step (A50h) was coupled with aminomethyltetrazole to afford the title product as acrystalline solid. MS found $(M+1)^+$ 734.4.

Example A52

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)- 3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide

Step (A52a) Following a procedure analogous to Step (A4a), the material from Step (A50k) was coupled with 3,5-dichlorophenyl-sulfonamide to give the title product. MS found $(M+1)^+$ 918.9.

Example A53

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide

Step (A53a) Following a procedure analogous to Step (A4a), the material from Step (A50k) was coupled with 2-chlorophenylsulfonamide to give the title product. MS found $(M+1)^+$ 883.3.

Example A54

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide

Following a procedure analogous to Step (A4a), the material from Step (A50k) was coupled with [5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonamide to give the title product. MS found $(M+1)^+$ 914.5.

Example A55

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-(3-aminosulfonyl-5-chlorophenyl)sulfonyl]glycinamide

Step (A55a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3-aminosulfonyl-5-chlorophenyl]sulfonamide to give the title product. MS found $(M+1)^+$ 962.4.

Example A56

(3S)-5,5,5-trifluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)- L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]- N-(2H-tetrazol-5-ylmethyl)pentanamide

Step (A56a): Following a procedure analogous to Steps (A1a-d), 2-hydroxyl-3-amino-5-trifluorovaleric acid methylester (Scheme1, **5** where R1=H, R2=CH2CF3, W"=OMe) was obtained. (A56b): Following a procedure analogous to Step (A1j), the product from (A56a) was coupled with the product from (A1I) to give the desired product (Scheme 4, **25a**).

(A56c): Following a procedure analogous to Steps (A2e-g), the material from Step (A56b) was converted to the desired product as a white solid (Scheme 6). MS found: (M+1)+ 752.9.

Example A57

N-[4-*sec*-butyl-15-{[(3-chloro-5-{[(3,3,3-trifluoropropanoyl)amino]sulfonyl}phenyl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A57a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with (3-chloro-5-{[(3,3,3-trifluoropropanoyl)amino]sulfonamide to give the title product. MS found $(M+1)^+$ 1073.4.

Example A58

N-[4-*sec*-butyl-15-[({3-chloro-5-[(hexanoylamino)sulfonyl]phenyl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A58a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with ({3-chloro-5-[(hexanoylamino)sulfonamide to give the title product. MS found $(M+1)^+$ 1061.3.

Example A59

N-[15-[([1,1'-biphenyl]-3-ylsulfonyl)amino]-4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A59a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with ([1,1'-

biphenyl]-3-yl] sulfonamide to give the title product. MS found $(M+1)^+$ 890.4.

Example A60

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-15-{[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide

Step (A60a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [(4'-methoxy[1,1'-biphenyl]-4-yl sulfonamide to give the title product. MS found $(M+1)^+$ 920.1.

Example A61

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-15-{[(3',5'-dichloro[1,1'-biphenyl]-4-yl)sulfonyl]amino}-10-ethyl-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide

Step (A61a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [(3',5'-dichloro[1,1'-biphenyl]-4-yl)sulfonamide to give the title product. MS found $(M+1)^+$ 958.5.

Example A62

N-[4-*sec*-butyl-15-{[(4'-chloro[1,1'-biphenyl]-3-yl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A62a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [(4'-chloro[1,1'-biphenyl]-3-yl)sulfonamide to give the title product. MS found $(M+1)^+$ 960.6.

Example A63

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-({[3-(2-methylphenoxy)phenyl]sulfonyl}amino)-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A63a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3-(2-methylphenoxy)phenyl]sulfonamide to give the title product. MS found $(M+1)^+$ 956.2.

Example A64

N-[4-*sec*-butyl-15-({[3-(2-chlorophenoxy)phenyl]sulfonyl}amino)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A64a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3-(2-chlorophenoxy)phenyl]phenyl]sulfonamide to give the title product. MS found $(M+1)^+$ 976.3.

Example A65

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13-pentaoxo-1-(2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid

Step (A65a): Following a procedure analogous to step (A4), the material from step (A50k) was treated with Dess-Martin reagent to obtained the title product. MS found $(M+1)^+$ 653.5.

Example A66

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-{[(4'-methyl[1,1'-biphenyl]-3-yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide

Step (A66a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [(4'-methyl[1,1'-biphenyl]-3-yl)sulfonamide to give the title product. MS found $(M+1)^+$ 940.1.

Example A67

N-[15-({[3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonyl}amino)-4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A67a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonamide to give the title product. MS found $(M+1)^+$ 1061.8.

Example A68

N-[4-*sec*-butyl-15-[({5-[(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A68a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with {[(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to give the title product. MS found $(M+1)^+$ 1001.9.

Example A69

N-[4-*sec*-butyl-15-[({5-[(2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A69a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with {5-[(2-

chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to give the title product. MS found $(M+1)^+$ 1011.2.

Example A70

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[({5-[(4-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

Step (A70a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with {5-[(4-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to give the title product. MS found $(M+1)^+$ 1006.8.

Example A71

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[({5-[(3-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

Step (A71a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with {5-[(3-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to give the title product. MS found $(M+1)^+$ 1007.1.

Example A72

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[({5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

Step (A72a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with {5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to give the title product. MS found $(M+1)^+$ 1007.1.

Example A73

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-15-{[(3-phenoxyphenyl)sulfonyl]amino}-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide

Step (A73a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with (3-phenoxyphenyl)sulfonamide to give the title product. MS found $(M+1)^+$ 941.8.

Example A74

6-*sec*-butyl-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-1,4,7,10,13-pentaoxo-1-(2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid

Step (A74a): Following a procedure analogous to step (A65a), the material from step (A50k) was treated with Dess-Martin reagent to give the title product. MS found $(M+1)^+$ 617.4.

Example A75

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[({5-[(3-methylbutanoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

Step (A75a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 957.0.

Example A76

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A76a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 971.0.

Example A77

Methyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oate

Step (A77a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 724.4.

Example A78

N-[4-*sec*-butyl-15-{[(3-chloro-5-{[(3-chlorobenzoyl)amino]sulfonyl}phenyl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A78a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 1066.1.

Example A79

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-15-({[4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonyl}amino)-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A79a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 993.9.

Example A80

N-[15-[([1,1'-biphenyl]-3-ylsulfonyl)amino]-4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A80a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 926.1.

Example A81

N-[4-*sec*-butyl-15-[({5-[(4-*tert*-butylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A81a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 1033.1.

Example A82

N-[4-*sec*-butyl-15-{[(3-chloro-5-{[(3-methylbutanoyl)amino]sulfonyl}phenyl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A82a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 1047.7.

Example A83

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-14-[4-(4-methoxyphenyl)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-3-yl]-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide

Step (A83a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 907.8.

Example A84

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-

yl}sulfonyl)amino]-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

Step (A84a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 1005.2.

Example A85

N-[4-*sec*-butyl-15-[({5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A85a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 1011.5.

Example A86

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-15-[({5-[(3,5-difluorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A86a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 1013.1.

Example A87

N-[4-*sec*-butyl-15-[({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A87a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found $(M+1)^+$ 1011.3.

Example A88

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide

Step (A88a): Following a procedure analogous to steps (A1) and (A4a). The detailed procedure can be found in Han, W. ect.; *Bioorg. Med. Chem. Lett. 10*, 711-713, **2000** and is hereby incorporated by reference in its entirety. The title compound was obtained. MS found $(M+1)^+$ 656.4.

Example A89

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-yn-1-yl}-2-pyrazinecarboxamide

Step (A89a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found $(M+1)^+$ 654.5.

Example A90

tert-butyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oate

Step (A90a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found $(M+1)^+$ 730.5.

Example A91

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-14-phenyl-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide

Step (A91a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found $(M+1)^+$ 706.4.

Example A92

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[((1*S*)-1-(cyclohexylmethyl)-2-{[(1*S*)-1-ethyl-2,3-dioxo-3-(1-pyrrolidinyl)propyl]amino}-2-oxoethyl)amino]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide

Step (A92a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found $(M+1)^+$ 670.3

Example A93

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-15,15,15-trifluoro-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

Step (A93a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found $(M+1)^+$ 698.2.

Example A94

N-{(1*S*,4*S*,7*S*,10*S*)-15-amino-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

Step (A94a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found $(M+1)^+$ 673.4.

Example A95

(3*S*,6*S*,9*S*,12*S*,16*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-16-methyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-

hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oic acid

Step (A95a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found $(M+1)^+$ 688.5.

Example A96

N-[9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-2,5,8,11,14-pentaoxo-14-(2-pyrazinyl)-4,7,10,13-tetraazatetradec-1-anoyl]aspartic acid

Step (A96a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found $(M+1)^+$ 732.4.

Example A97

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaoctadecan-18-oic acid

Step (A97a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found $(M+1)^+$ 688.5.

Example B1

1,1-dimethylethyl N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L- prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine

Step (B1a): Following a procedure analogous to step (A1) and (A50), the compound **32a** {Pz(CO)-Lue-Ile-Hyp(OBn)-NHCH(CH_2CHF_2)CH(OH)CO_2Me} was obtained as crystalline solid. MS found $(M+1)^+$ 719.1.

Step (B1b): Following a procedure analogous to step (A2e), the product from step (B1a) was treated with LiOH to

provide the corresponding α-hydroxyacid as crystalline solid. MS found $(M+1)^+$ 715.1; $(M-1)^-$ 713.

Step (B1c): Following a procedure analogous to step (A1j) and step (A1k), the above material was coupled with Gly-OtBu followed by oxidation to provide the title product (Scheme 5, **33**) as crystalline solid. MS found $(M+1)^+$ 816.4.

Example B2

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-di fluoro-2-oxo-(3S)-3-aminopentanoylglycine

Step (B2a): Following a procedure analogous to Step (A1l), the material from Step (B1c) was treated with TFA to afford title product (Scheme 5, **34**) as a white solid. MS found $(M+1)^+$ 760.3.

Example B3

(4R)-1-[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl]- N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H)-tetrazol-5-yl methyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide

Step (B3a): Following a procedure analogous to Steps (A2f-g), the material from Step (B1b) was coupled with aminotetrazole followed by oxidation to give the title product as a white solid. MS found $(M+1)^+$ 784.4.

Example B4

(4R)-N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-3-methoxy-2,3-dioxopropyl]-4-(phenylmethoxy)-L-prolinamide

Step (B4a): Following a procedure analogous to step (A2g), the material from (B1a) was oxidized to the desired product. MS found $(M+1)^+$ 717.3.

Example B5

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide

Step (B5a): Following a procedure analogous to Step (A4a), the material from Step (B2a) was coupled with 3-chlorophenylsulfonamide to afford the title product as a white solid. MS found $(M+1)^+$ 933.3.

Example B6

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-carboxy-2-chlorophenyl)-sulfonyl]glycinamide

Step (B6a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with 5-carboxy-2-chlorophenylsulfonamide to afford title product as white solid. MS found $(M+1)^+$ 978.2

Example B7

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-acetylamino)1,3,4-thiadiazol-2-yl)sulfonyl]glycinamide

Step (B7a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with N-[(5-acetylamino)1,3,4-thiadiazol-2-yl)sulfonamide to afford title product as white solid. MS found $(M+1+H_2O)^+$ 982.5.

Example B8

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[3,5-dichlorophenyl) sulfonyl]glycinamide

Step (B8a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (3,5-dichlorophenyl) sulfonamide to afford title product as white solid. MS found $(M+1)^+$ 967.6.

Example B9

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-(4-methyl-3-nitrophenyl)sulfonyl]-glycinamide

Step (B9a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (4-methyl-3-nitrophenyl) sulfonamide to afford title product as white solid. MS found $(M+1)^+$ 958.4.

Example B10

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-(3-carboxyl-4-chloro-2-fluorophenyl)sulfonyl]-glycinamide

Step (B10a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (3-carboxyl-4-chloro-2-fluorophenyl)sulfonamide to afford title product as white solid. MS found $(M+1)^+$ 995.4.

Example B11

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-[(3-chloro-4-acetylamino)phenyl]sulfonyl]-glycinamide

Step (B11a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (3-chloro-4-

acetylamino)phenyl sulfonamide to afford title product as white solid. MS found $(M+1)^+$ 1116.5.

Example B12

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[(2*S*,4*R*)-2-({[(1*S*)-3-({2-[({3-[(benzoylamino)sulfonyl]-5-chlorophenyl}sulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]amino}carbonyl)-4-(benzyloxy)pyrrolidinyl]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide

Step (B12a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 1117.4.

Example B13

tert-butyl ({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*)-3-methyl-2-({(2*S*)-3-methyl-2-[(2-pyrazinylcarbonyl)amino]butanoyl}amino)butanoyl]pyrrolidinyl}carbonyl)amino]-5,5-difluoro-2-oxopentanoyl}amino)acetate

Step (B13a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 788.9.

Example B14

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[(2*S*,4*R*)-4-(benzyloxy)-2-({[(1*S*)-3-[(2-{[(3-chloro-4-methylphenyl)sulfonyl]amino}-2-oxoethyl)amino]-1-(2,2-difluoroethyl)-2,3-dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide

Step (B14a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 948.3.

Example B15

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[(2*S*,4*R*)-4-(benzyloxy)-2-({[(1*S*)-3-({2-[({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide

Step (B15a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 1061.3.

Example B16

Methyl ({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-methyl-2-({(2*S*)-4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]pyrrolidinyl}carbonyl)amino]-5,5-difluoro-2-oxopentanoyl}amino)acetate

Step (B16a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 774.6.

Example B17

N-((1*S*)-1-{[((1*S*,2*R*)-1-{[(2*S*,4*R*)-4-(benzyloxy)-2-({[(1*S*)-3-[(2-{[(2,4-dichloro-5-methylphenyl)sulfonyl]amino}-2-oxoethyl)amino]-1-(2,2-difluoroethyl)-2,3-dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide

Step (B17a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 982.6.

Example B18

N-[(1*S*)-1-({[((1*S*,2*R*)-1-({(2*S*,4*R*)-4-(benzyloxy)-2-[({(1*S*)-1-(2,2-difluoroethyl)-3-[(2-{[(3,4-difluorophenyl)sulfonyl]amino}-2-oxoethyl)amino]-2,3-dioxopropyl}amino)carbonyl]pyrrolidinyl}carbonyl)-2-

methylbutyl]amino}carbonyl)-3-methylbutyl]-2-pyrazinecarboxamide

Step (B18a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 935.7.

Example B19

Methyl 5-({[({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-methyl-2-({(2*S*)-4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]pyrrolidinyl}carbonyl)amino]-5,5-difluoro-2-oxopentanoyl}amino)acetyl]amino}sulfonyl)-2,4-dichlorobenzoate

Step (B19a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 1026.7.

Example B20

N-{(1*S*)-1-[({(1*S*,2*R*)-1-[((2*S*,4*R*)-4-(benzyloxy)-2-{[((1*S*)-1-(2,2-difluoroethyl)-3-{[2-({[4-(3,5-dimethyl-1-piperidinyl)-3-nitrophenyl]sulfonyl}amino)-2-oxoethyl]amino}-2,3-dioxopropyl)amino]carbonyl}pyrrolidinyl)carbonyl]-2-methylbutyl}amino)carbonyl]-3-methylbutyl}-2-pyrazinecarboxamide

Step (B20a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 1056.0.

Example B21

N-[(1*S*)-1-({[(1*S*,2*R*)-1-({(2*S*,4*R*)-4-(benzyloxy)-2-[({(1*S*)-1-(2,2-difluoroethyl)-3-[(2-{[(3-nitrophenyl)sulfonyl]amino}-2-oxoethyl)amino]-2,3-dioxopropyl}amino)carbonyl]pyrrolidinyl}carbonyl)-2-methylbutyl]amino}carbonyl)-3-methylbutyl]-2-pyrazinecarboxamide

Step (B21a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 944.8.

Example B22

N-{(1*S*)-1-[({(1*S*,2*R*)-1-[((2*S*,4*R*)-4-(benzyloxy)-2-{[((1*S*)-1-(2,2-difluoroethyl)-3-{[2-({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-2,3-dioxopropyl)amino]carbonyl}pyrrolidinyl)carbonyl]-2-methylbutyl}amino)carbonyl]-3-methylbutyl}-2-pyrazinecarboxamide

Step (B22a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 1021.1.

Example B23

5-({[({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-methyl-2-({(2*S*)-4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]pyrrolidinyl}carbonyl)amino]-5,5-difluoro-2-oxopentanoyl}amino)acetyl]amino}sulfonyl)-2,4-dichlorobenzoic acid

Step (B23a): Following a procedure analogous to step (B7a), the title compound was obtained. MS found $(M+1)^+$ 1012.6.

Example C1

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoylglycine

Step (C1a): Following the procedures analogous to step (A1) and step (A2), the title product was obtained as crystalline solid. MS found $(M+1)^+$ 659.4.

Example C2

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(trifluoromethyl)sulfonyl]glycinamide

Step (C2a): Following a procedure analogous to step (A4a), the material from step (C1a) was coupled with trifluoromethylsulfonamide to afford the title product as crystalline solid. MS found $(M+1)^+$ 790.3.

Example C3

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide

Step (C3a): Following the procedures analogous to step (A4a), the material from step (C1a) was coupled with 3,5-dichlorophenyl)sulfonamide to afford the title product as crystalline solid. MS found $(M+1)^+$ 866.6.

Example C4

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3-nitrophenyl)sulfonyl]glycinamide

Step (C4a): Following the procedures analogous to step (A4a), the material from step (C1a) was coupled with -[(3-nitrophenyl)sulfonamide to afford the title product as crystalline solid. MS found $(M+1)^+$ 841.3.

Example C5

(4R)-1-[[5-(4-chlorophenyl)-2-furanyl]carbonyl-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H-tetrazol-5-ylmethyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide

Step (C5a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found $(M+1)^+$ 769.3.

Example C6

(2*S*,4*R*)-4-(benzyloxy)-*N*-{(1*S*)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2*H*-tetraazol-5-ylmethyl)amino]propyl}-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

Step (C6a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found $(M+1)^+$ 771.5.

Example C7

tert-butyl {[(3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetate

Step (C7a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found $(M+1)^+$ 803.4.

Example C8

{[(3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetic acid

Step (C8a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found $(M+1)^+$ 747.3.

Example C9

(2*S*,4*R*)-*N*-[(1*S*)-3-{[2-({[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

Step (C9a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found $(M+1)^+$ 951.2.

Example C10

(2*S*,4*R*)-4-(benzyloxy)-*N*-((1*S*)-1-(2,2-difluoroethyl)-3-{[2-({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-2,3-dioxopropyl)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

Step (C10a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found $(M+1)^+$ 1007.9.

Example C11

((2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[({5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

Step (C11a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found $(M+1)^+$ 1048.3.

Example C12

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-1-(2,2-difluoroethyl)-3-({2-[({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2-oxoethyl}amino)-2,3-dioxopropyl]-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

Step (C12a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found $(M+1)^+$ 1041.8.

Example C13

tert-butyl {[(3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetate

Step (C13a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained. MS found $(M+1)^+$ 801.9.

Example C14

{[(3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetic acid

Step (C14a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained. MS found $(M+1)^+$ 746.0.

Example C15

(2*S*,4*R*)-*N*-[(1*S*)-3-{[2-({[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide

Step (C15a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained. MS found $(M+1)^+$ 950.1.

Example C16

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-

((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide

Step (C16a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained. MS found $(M+1)^+$ 1046.7.

Example C17

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[([1,1'-biphenyl]-3-ylsulfonyl)amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide

Step (C17a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained. MS found $(M+1)^+$ 961.2.

Example D1

N-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide

Step (D1a): The α-hydroxyl β-allyl homoallylglycinamide was prepared according to the following reference disclosed in Han, W. et. al, *Bioorg. & Med. Chem Lett.*, *10*, 711-713, **2000**, which is hereby incorporated by reference.

(D1b): Tripeptide R-Leu-Ile-Cha-OH was prepared following a procedure analogous to Steps (A2a-h).

(D1c): Following a procedure analogous to Step (A1j), the product from (D1a) and (D1b) was coupled to give the desired α-hydroxyamide.

(D1d): Following a procedure analogous to Step (A2g), the above α-hydroxyamide was converted to the desired product. MS found (M+1)+ 668.3.

Example D2

(6*S*,9*S*,12*S*)-*N*,3-diallyl-6-(cyclohexylmethyl)-12-isobutyl-9-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-tetraazahexadecan-1-amide

Step (D2a): Following a procedure analogous to Steps (D1a-d), the title compound was obtained. MS found $(M+1)^+$ 770.9.

Example D3

(4*S*,7*S*,10*S*)-*N*,13-diallyl-10-(cyclohexylmethyl)-4-isobutyl-7-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-3,6,9,12-tetraazapentadecan-15-amide

Step (D3a): Following a procedure analogous to Steps (D1a-d), the title compound was obtained. MS found $(M+1)^+$ 604.1.

Example D4

N-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-2-pyridinecarboxamide

Step (D4a): Following a procedure analogous to to Steps (D1a-d), the title compound was obtained. MS found $(M+1)^+$ 667.4.

Example D5

N-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}nicotinamide

Step (D5a): Following a procedure analogous to to Steps (D1a-d), the title compound was obtained. MS found $(M+1)^+$ 667.4.

Example D6

N-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-

tetraazahexadec-15-en-1-yl}-4-nitro-1*H*-pyrazole-3-carboxamide

Step (D6a): Following a procedure analogous to to Steps (D1a-d), the title compound was obtained. MS found $(M+1)^+$ 701.5.

Example D7

2-{(3*S*,6*S*,9*S*)-12-allyl-9-(cyclohexylmethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-4,7,10,13,14-pentaoxo-2,5,8,11,15-pentaazaoctadec-17-en-1-anoyl}benzoic acid

Step (D7a): Following a procedure analogous to to Steps (D1a-d), the title compound was obtained. MS found $(M+1)^+$ 710.3.

Example D8

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl]nicotinamide

(D8a): Following a procedure analogous to Step (Alj), the product from (D1b) was coupled with the product from (Ald) to give the desired a-hydroxyester.
(D8b): Following a procedure analogous to Steps (A2e-g), the material from Step (D8a) was converted to the desired product as a white solid (Scheme 6). MS found: (M+1)+ 656.4.

Example D9

N-allyl-9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-tetraazahexadecan-1-amide

Step (D9a): Following a procedure analogous to Step (D8a-b), the title compound was obtained. MS found $(M+1)^+$ 758.8.

Example D10

({3-[({1-[3-methyl-2-({4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]-octahydro-1*H*-indol-2-yl}carbonyl)amino]-2-oxopentanoyl}amino)acetic acid

(D10a): The peptide pyrizinecarbonyl-Leu-Ile-octahydroindazole carboxylic acid was prepared following a procedure analogous to Steps (A2a-h).

(D10b): Following a procedure analogous to Steps (A1j-l), the above peptide was coupled with the product from (A1d) and converted to the desired product. MS found (M+1)+ 672.4.

Example D11

tert-butyl ({3-[({1-[3-methyl-2-({4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)-pentanoyl]octahydro-1*H*-indol-2-yl}carbonyl)amino]-2-oxopentanoyl}amino)acetate

Step (D11a): Following a procedure analogous to Steps (D10a-b), the title compound was obtained. MS found $(M+1)^+$ 728.5.

Example D12

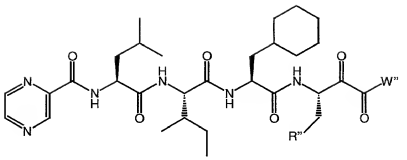
(3*S*,6*S*,9*S*,12*S*)-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-9-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-tetraazahexadecan-1-oic acid

(D12a): Tripeptide R-Leu-Ile-Cha-OH was prepared following a procedure analogous to Steps (A2a-h).

(D12b): Following a procedure analogous to Step (A1j), the above tripeptide was coupled to the product from (A1d) to give the desired a-hydroxyester.

((D12c): Following a procedure analogous to Steps (A2e) and (A2g), the above material was converted to the desired product. MS found (M+1)+ 719.6.

Table 1

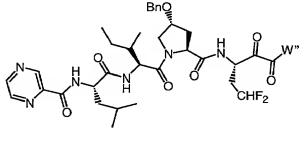


Ex #	R"	W"	(M+1)+
A1	Me	Glycine	674.4
A2	Me	2H-tetrazol-5-yl-methylamino	698.4
A3	Me	Sulfonylmethylamino	710.3
A4	Me	N-[(3-nitrophenyl)sulfonyl]-glycinamide	858.3
A5	Me	N-(methylsulfonyl)glycinamide	751.4
A6	Me	N-[(phenylmethyl)sulfonyl]-glycinamide	825.4
A7	Me	N-(phenylsulfonyl)glycinamide	813.4
A8	Me	N-[(trifluoromethyl)sulfonyl]-glycinamide	805.4
A9	Me	N-[(2-nitrophenyl)-sulfonyl]glycinamide	858.1
A10	Me	N-[(4-nitrophenyl)sulfonyl]-glycinamide	858.3
A11	Me	N-[(4-fluorophenyl)sulfonyl]-glycinamide	831.4
A12	Me	N-[(3-fluorophenyl)sulfonyl]-glycinamide	831.4
A13	Me	N-[(2-fluorophenyl)sulfonyl]-glycinamide	831.5
A14	Me	N-[(4-chlorophenyl)sulfonyl]-glycinamide	848.3
A15	Me	N-[(3-chlorophenyl)sulfonyl]-glycinamide	848.4
A16	Me	N-[[4-(thionitroso)phenyl]sulfonyl]glycinamide	870.6
A17	Me	N-[[4-[(trifluoromethyl)sulfonyl]-phenyl]-sulfonyl]glycinamide	946.1
A18	Me	N-[[4-(trifluoromethyl)-phenyl]-sulfonyl]-glycinamide	881.8
A19	Me	N-[(4-cyanophenyl)sulfonyl]-glycinamide	839.0
A20	Me	N-[(3-chloro-4-methylphenyl)-sulfonyl]-glycinamide	862.3
A21	Me	N-[(4-chloro-3-nitrophenyl)-sulfonyl]-glycinamide	893.4
A22	Me	N-[(3,5-dichlorophenyl)sulfonyl]-glycinamide	882.9
A23	Me	N-[(4-methyl-3-nitrophenyl)sulfonyl]-glycinamide	873.1
A24	Me	N-[[2-chloro-5-(trifluoromethyl)-phenyl]-sulfonyl]glycinamide	916.5
A25	Me	N-[(5-carboxy-2-chlorophenyl)sulfonyl]-glycinamide	892.3
A26	Me	N-[(2,5-dichlorophenyl)-sulfonyl]-glycinamide	879.5
A27	Me	N-[(3,4-difluorophenyl)-sulfonyl]-glycinamide	849.6
A28	Me	N-[(3,5-dichloro-2-hydroxyphenyl)-sulfonyl]-glycinamide	895.5 (M-1)-
A29	Me	N-[(2,4,5-trichlorophenyl)sulfonyl]glycinamide	913.3 (M-1)-
A30	Me	N-[(5-carboxy-4-chloro-2-fluorophenyl)-sulfonyl]glycinamide	910.6
A31	Me	N-[[5-(dimethylamino)-1-naphthalenyl]-sulfonyl]-glycinamide	907.3
A32	Me	N-(2-naphthalenylsulfonyl)-glycinamide	864.2
A33	Me	N-[(4-(phenyl)phenyl]sulfonyl]glycinamide	889.5
A34	Me	N-[(6-ethoxy-2-benzothiazolyl-sulfonyl]-glycinamide	915.2

A35	Me	N-[[2-chloro-5-[[(phenylmethyl)-amino]-carbonyl]phenyl]-sulfonyl]glycinamide	980.6
A36	Me	N-[[2-chloro-5-[[(2-trifluoroethyl)-amino]carbonyl]-phenyl]-sulfonyl]glycinamide	970.5 (M-1)-
A37	Me	N-[[2-chloro-5-[[(cyclopropylmethyl)amino]-carbonyl]phenyl]sulfonyl]glycinamide	944.4
A38	Me	N-[[3-nitro-4-(2-pyrimidinylthio)-phenyl]sulfonyl]glycinamide	968.4
A39	Me	N-[[2-chloro-4-(acetylamino)-phenyl]sulfonyl]glycinamide	902.5 (M-1)-
A40	Me	N-[[3-chloro-4-(2-benzoxazolylthio)phenyl]-sulfonyl]glycinamide	1005.5 (M-1)-
A41	Me	N-[[3,5-dichloro-4-(4-nitrophenoxy)phenyl]-sulfonyl]glycinamide	1018.5
A42	Me	N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]-sulfonyl]-glycinamide	878.5
A43	Me	N-[(3-cyanophenyl)-sulfonyl]-glycinamide	838.4
A44	Me	N-[[3-(aminosulfonyl)-5-chlorophenyl]-sulfonyl]glycinamide	924.4 (M-1)-
A45	Me	N-[[3,5-bis(trifluoromethyl)-phenyl]-sulfonyl]glycinamide	949.4
A46	Me	N-{4-[5-(3-(4-chlorophenyl)-3-oxo-1-propenyl)2-furanyl]-phenyl}sulfonyl glycinamide	1043.5
A47	Me	3{[benzylamino]carbonylphenyl-sulfonyl}-glycinamide	946.6
A48	Me	N-[[[[(2-trifluoroethyl)-amino]-carbonyl]phenyl]sulfonyl]-glycinamide	938.5
A49	Me	N-[[3-[(benzolamino)-sulfonyl]-5-chlorophenyl]-sulfonyl]glycinamide	1030.6
A50	CHF_2	glycine	710.4
A51	CHF_2	2H-tetrazol-5-yl-methylamino	734.4
A52	CHF_2	N-[(3,5-dichlorophenyl)-sulfonyl]-glycinamide	918.9
A53	CHF_2	N-[(3-chlorophenyl)-sulfonyl]-glycinamide	883.3
A54	CHF_2	N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide	914.5
A55	CHF_2	N-[3-aminosulfonyl-5-chlorophenyl]sulfonyl-glycinamide	962.4
A56	CF_3	2H-tetrazol-5-yl-methylamino	752.9
A57	CHF_2	N-{[(3-chloro-5-{[(3,3,3-trifluoropropanoyl)amino]sulfonyl}phenyl)sulfonyl}glycinamide	1073.4
A58	CHF_2	N-[({3-chloro-5-[(hexanoylamino)sulfonyl]phenyl}sulfonyl)}glycinamide	1061.3
A59	Me	*N*-[[1,1'-biphenyl]-3-ylsulfonyl] glycinamide	890.4
A60	Me	N-[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl] glycinamide	920.1
A61	Me	N-[(3',5'-dichloro[1,1'-biphenyl]-4-yl)sulfonyl] glycinamide	958.5
A62	CHF_2	N-[(4'-chloro[1,1'-biphenyl]-3-yl)sulfonyl] glycinamide	960.6
A63	CHF_2	N-{4-(2-methylphenoxy)phenyl]sulfonyl} glycinamide	956.2
A64	CHF_2	N-{[3-(2-chlorophenoxy)phenyl]sulfonyl} glycinamide	976.3
A65	CHF_2	OH	653.5
A66	CHF_2	N-[(4'-methyl[1,1'-biphenyl]-3-yl)sulfonyl] glycinamide	940.1
A67	CHF_2	N-({[3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonyl} glycinamide	1061.8
A68	CHF_2	N-({5-[(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1001.9

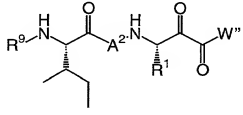
A69	CHF_2	N-({5-[(2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1011.2
A70	CHF_2	N-({5-[(4-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1006.8
A71	CHF_2	N-({5-[(3-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1007.1
A72	CHF_2	N-{5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1004.8
A73	CHF_2	N-[(3-phenoxyphenyl)sulfonyl] glycinamide	941.8
A74	Me	OH	617.4
A75	CHF_2	N-({5-[(3-methylbutanoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	957.0
A76	CHF_2	N-({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl glycinamide	971.0
A77	CHF_2	methyloxy glycine	724.4
A78	Me	N-[(3-chloro-5-{[(3-chlorobenzoyl)amino]sulfonyl glycinamide	1066.1
A79	CHF_2	N-{[4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonyl}glycinamide	993.9
A80	CHF_2	N-[([1,1'-biphenyl]-3-ylsulfonyl] glycinamide	926.1
A81	CHF_2	N-({5-[(4-*tert*-butylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1033.1
A82	CHF_2	N-[(3-chloro-5-{[(3-methylbutanoyl)amino]sulfonyl}phenyl)sulfonyl] glycinamide	1047.7
A83	CHF_2	4-(4-methoxyphenyl)-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl-methylamino	907.8
A84	CHF_2	N-({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1005.2
A85	CHF_2	N-({5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1011.5
A86	CHF_2	N-({5-[(3,5-difluorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1013.1
A87	CHF_2	N-({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1011.3
A88	Me	allylamino	656.4
A89	Me	propargylamino	654.5
A90	Me	t-butyloxy glycine	730.5
A91	Me	benzylamino	706.4
A92	Me	N-pyrrolidinyl	670.3
A93	Me	1,1,1-trifluoroethylamino	698.2
A94	Me	glycinamide	673.4
A95	Me	L-alanine	688.5
A96	Me	L-aspartic acid	732.4
A97	Me	homoglycine	688.5

Table 2



Ex #	W"	(M+1)+
B1	Tert-butyl glycine	816.4
B2	Glycine	760.3
B3	Aminomethyltetrazole	784.4
B4	Methoxyl	717.3
B5	N-[(3-chlorophenyl)-sulfonyl]-glycinamide	933.3
B6	N-[(5-carboxy-2-chlorophenyl)-sulfonyl]glycinamide	978.2
B7	N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide	982.5 (M+1+H_2O)+
B8	N-[(3,5-dichlorophenyl)-sulfonyl]-glycinamide	967.6
B9	N-[(4-methyl-3-nitrophenyl)-sulfonyl]glycinamide	958.4
B10	N-[(3-carboxyl-4-chloro-2-fluorophenyl)sulfonyl]-glycinamide	995.4
B11	N-[[3-chloro-4-(acetylamino)-phenyl]sulfonyl]glycinamide	1116.5
B12	N-({3-[(benzoylamino)sulfonyl]-5-chlorophenyl}sulfonyl) glycinamide	1117.4
B13	Glycine t-Butylester	788.9
B14	N-[(3-chloro-4-methylphenyl)sulfonyl] glycinamide	948.3
B15	N-({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl) glycinamide	1061.3
B16	Glycine methylester	774.6
B17	N-[(2,4-dichloro-5-methylphenyl)sulfonyl] glycinamide	982.6
B18	N-[(3,4-difluorophenyl)sulfonyl] glycinamide	935.7
B19	N-[(3,4-dichlorophenyl)sulfonyl] glycinamide	1026.7
B20	N-{[4-(3,5-dimethyl-1-piperidinyl)-3-nitrophenyl]sulfonyl} glycinamide	1056.0
B21	N-[(3-nitrophenyl) sulfonyl] glycinamide	944.8
B22	N-{[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl} glycinamide	1021.1
B23	N-[(2,4-dichloro-5-carboxylphenyl) sulfonyl] glycinamide	1012.6

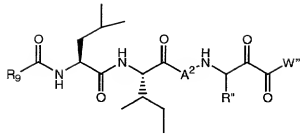
Table 3



Ex#	R^9	A^2	R^1	W"	$(M+1)^+$
C1	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	glycine	659.4

C2	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	N-(trifluoro-methyl-sulfonyl)-glycinamide	790.3
C3	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	N-(3,5-dichloro-phenyl-sulfonyl)-glycinamide	866.6
C4	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	N-(3-nitrophenyl-sulfonyl)glycinamide	841.3
C5	4-chlorophenyl-2-furanylcarbonyl	HyPOBn	CH_2CHF_2	aminomethyl tetrazole	769.3
C6	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	2*H*-tetrazol-5-yl-methylamino-	771.5
C7	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	Gly(OtBu)	803.4
C8	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	Glycine	747.3
C9	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	N-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}glycinamide	951.2
C10	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	N-{[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}glycinamide	1007.9
C11	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	N-({5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)glycinamide	1048.3
C12	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	N-({2-[({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)glycinamide	1041.8
C13	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	Gly(OtBu)	801.9
C14	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	Glycine	746.0
C15	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	N-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}glycinamide	950.1
C16	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	N-({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)glycinamide	1046.7
C17	[(9-oxo-9*H*-fluoren-1-yl)carbonyl	HyPOBn	CH_2CHF_2	N-([1,1'-biphenyl]-3-ylsulfonyl)glycinamide	961.2

Table 4



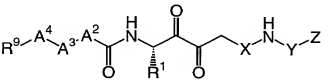
EX#	R9	A2	R"	W"	(M+1)+
D1	Pyrazine carbonyl	Cha	allyl	allylamino	668.3
D2	3,3-diphenyl propionyl	Cha	allyl	allylamino	770.9
D3	Acetyl	Cha	allyl	allylamino	604.1
D4	2-pyridine carbonyl	Cha	allyl	allylamino	667.4
D5	3-pyridine carbonyl	Cha	allyl	allylamino	667.4
D6	4-nitropyrazole carbonyl	Cha	allyl	allylamino	701.5
D7	2-carboxyl benzoyl	Cha	allyl	allylamino	710.3
D8	3-pyridine carbonyl	Cha	ehtyl	allylamino	655.4
D9	3,3-diphenyl propionyl	Cha	ethyl	allylamino	758.8
D10	Pyrazine carbonyl	Octahydro indazole 2-carboxylic acid	ethyl	glycine	672.4
D11	Pyrazine carbonyl	Octahydro indazole 2-carboxylic acid	ethyl	Glycine t-butylester	728.5
D12	3,3-diphenyl propionyl	Cha	ethyl	hydroxyl	719.6

The following Table 5 contains representative examples envisioned by the present invention. At the start of each table is one formula followed by species **Z1** through **Z67** demonstrating the intended substitution of Z; species **1a** through **1bw** demonstrating the intended substitution of R^1; and species **9a** through **9n** demonstrating the intended substitution of R^9. Each entry in each table is intended to be paired with each formula at the start of the table. For example, Example 100 in Table 5 is intended to be paired with each of formulae **Z1, Z2, Z3, Z4, ...** through **Z67** of Table 4, as well as each of formulae **1a, 1b, 1c, 1d,**

... through **1bw** of Table 4, as well as each of formulae **9a, 9b, 9c, 9d, ...** through **9n** of Table 4; thereby representing Example 100-9a-1a-Z1, 100-9a-1a-Z2, 100-9a-1a-Z3, ... through 243-9n-1bw-Z67.

As an illustration, Example 100-9a-1a-Z1 is N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-(methylsulfonyl) glycinamide.

Table 5



Z is selected from:

Z1:	methyl	**Z21:**	ethyl
Z2:	propyl	**Z22:**	trifluoromethyl
Z3:	phenyl	**Z23:**	benzyl
Z4:	4-phenyl-phenyl	**Z24:**	4-NCS-phenyl
Z5:	2-fluorophenyl-	**Z25:**	3-fluorophenyl-
Z6:	4-fluorophenyl-	**Z26:**	2-chlorophenyl-
Z7:	3-chlorophenyl-	**Z27:**	4-chlorophenyl-
Z8:	2-cyanophenyl-	**Z28:**	3-cyanophenyl-
Z9:	4-cyanophenyl-	**Z29:**	2-nitrophenyl-
Z10:	3-nitrophenyl-	**Z30:**	4-nitrophenyl-
Z11:	2-CF_3SO_2-phenyl-	**Z31:**	3-CF_3SO_2-phenyl-
Z12:	4-CF_3SO_2-phenyl-	**Z32:**	2-CF_3-phenyl-
Z13:	3-CF_3-phenyl-	**Z33:**	4-CF_3-phenyl-
Z14:	3-NO_2-4-Cl-phenyl-	**Z34:**	3-Cl-4-CH_3-phenyl-
Z15:	2-Cl-5-CF_3-phenyl-	**Z35:**	2-Cl-5-CO_2H-phenyl-
Z16:	3-NO_2-4-CH_3-phenyl-	**Z36:**	3-Cl-5-NH_2SO_2-phenyl-
Z17:	3,5-diCF_3-phenyl-	**Z37:**	3,4-diCF_3-phenyl-
Z18:	3,5-diCl-phenyl-	**Z38:**	2,5-diCl-phenyl-
Z19:	3,4-diCl-phenyl-	**Z39:**	3,5-diF-phenyl-
Z20:	2,5-diF-phenyl-	**Z40:**	3,4-diF-phenyl-

Z41: 2-F-4-Cl-5-CO_2H-phenyl-
Z42: 2,4-diCl-5-CO_2H-phenyl-
Z43: 2,4-diCl-5-CH_3CO_2-phenyl-
Z44: 2,4-diCl-5-CH_3-phenyl-
Z45: 2-OH-3,5-diCl-phenyl-
Z46: 2,4,5-triCl-phenyl-
Z47: 3,5-diCl-4-(4-NO_2phenyl)phenyl-
Z48: 2-Cl-5-benzyl-NHCO-phenyl-
Z49: 2-Cl-5-CF_3CH_2-NHCO-phenyl-
Z50: 2-Cl-5-cyclopropylmethyl-NHCO-phenyl-
Z51: 2-Cl-4-CH_3CONH-phenyl-
Z52: 5-CH_3CONH-1*H*-pyrrol-2-yl-
Z53: 5-phenylCONH-furan-2-yl-
Z54: 2-CH_3CONH-2,3-dihydrofuran-5-yl-

Z55: 3-Cl-5-(phenylCONHSO$_2$)-phenyl-
Z56: 3-Cl-5-CH$_3$CONH-phenyl-
Z57: 5-ethoxy-benzothiazol-2-yl
Z58: naphth-2-yl
Z59: (CH$_3$CONH)thiadiazolyl-
Z60: (s-butyl-CONH)-thiadiazolyl-
Z61: (n-pentyl-CONH)thiadiazolyl-
Z62: (phenyl-CONH)-thiadiazolyl-
Z63: (3-Cl-phenyl-CONH)thiadiazolyl-
Z64: (benzoxazol-2-yl)-
Z65: (1*H*-benzimidazol-2-yl)-
Z66: thiazolo[4,5-c]pyrid-2-yl-
Z67: 9H-purin-8-yl

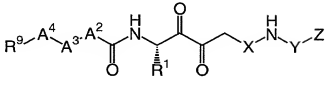
R^1 is selected from:

1a: -CH$_2$CH$_3$
1b: -CH$_2$CH$_2$CH$_3$
1c: -CH(CH$_3$)$_2$
1d: -CH$_2$CH$_2$CH$_2$CH$_3$
1e: -CH$_2$CH(CH$_3$)$_2$
1f: -CH$_2$C(CH$_3$)$_3$
1g: -CH$_2$CH$_2$C(CH$_3$)$_3$
1h: -CH$_2$CF$_3$
1i: -CH$_2$CH$_2$CF$_3$
1j: -CH$_2$CH$_2$CH$_2$CF$_3$
1k: -CH$_2$CH=CH$_2$
1l: cis-CH$_2$CH=CH(CH$_3$)
1m: -CH$_2$CH$_2$CH=CH
1n: -CH$_2$CH$_2$CH=C(CH$_3$)$_2$
1o: benzyl
1p: phenpropyl
1q: -CH$_2$CO$_2$H
1r: -CH$_2$CO$_2$C(CH$_3$)$_3$
1s: -CH$_2$CH$_2$CH$_2$CH$_2$NH$_2$
1t: (cyclobutyl)methyl-
1u: (cyclobutyl)propyl-
1v: cyclobutyl
1w: cyclohexyl
1x: (2-methylphenyl)ethyl-
1y: (3-methylphenyl)ethyl-
1z: (4-methylphenyl)ethyl-
1aa: (2-fluorophenyl)ethyl-
1ab: (3-fluorophenyl)ethyl-
1ac: (4-fluorophenyl)ethyl-
1ad: (2-bromophenyl)ethyl-
1ae: (4-bromophenyl)ethyl-
1af: (4-phenyl-phenyl)ethyl-
1ag: (2,4-dimethylphenyl)ethyl-
1ah: -CH$_2$CH$_2$CH$_2$C(CH$_3$)$_3$
1ai: -CH$_2$CH$_2$CH$_2$CH(CH$_3$)$_2$
1aj: -CH$_2$CH$_2$CH$_2$CH(CH$_2$CH$_3$)$_2$
1ak: -CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$
1al: -CH$_2$CH$_2$CH(CH$_3$)$_2$
1am: -CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$
1an: -CH$_2$CHF$_2$
1ao: -CH$_2$CH$_2$CHF$_2$
1ap: -CH$_2$CH$_2$CH$_2$CHF$_2$
1aq: -CH=CH$_2$
1ar: -CH=CHCH$_3$
1as: trans-CH$_2$CH=CH(CH$_3$)
1at: -CH$_2$CH=C(CH$_3$)$_2$
1au: phenyl
1av: phenethyl
1aw: phenbutyl
1ax: -CH$_2$CH$_2$CO$_2$H
1ay: -CH$_2$CH$_2$CO$_2$C(CH$_3$)$_3$
1az: (naphth-2-yl)ethyl-
1ba: (cyclobutyl)ethyl-
1bb: cyclopropyl
1bc: cyclopentyl
1bd: (4-ethylphenyl)ethyl-
1be: (4-i-propylphenyl)ethyl-
1bf: (4-t-butylphenyl)ethyl-
1bg: (4-hydroxyphenyl)ethyl-
1bh: (2-chlorophenyl)ethyl-
1bi: (3-chlorophenyl)ethyl-
1bj: (4-chlorophenyl)ethyl-
1bk: (3-bromophenyl)ethyl-
1bm: (4-phenoxy-phenyl)ethyl-
1bn: (2,5-dimethylphenyl)ethyl-
1bo: (2,6-difluorophenyl)ethyl-
1bp: (4-cyclohexyl-phenyl)ethyl-
1bq: (4-cyclopentyl-phenyl)ethyl-
1br: (4-cyclobutyl-phenyl)ethyl-
1bs: (4-cyclopropyl-phenyl)ethyl-
1bt: (2-trifluoromethylphenyl)ethyl-
1bu: (3-trifluoromethylphenyl)ethyl-
1bv: (4-trifluoromethylphenyl)ethyl-
1bw: (2,3,4,5,6-pentafluorophenyl)ethyl-

R^9 is selected from:

9a: 2-pyrazinyl-CO-
9b: 4-(N-pyrrolyl)phenyl-CO-
9c: 5-(4-Cl-phenyl)furan-2-yl-CO-
9d: 1-anthracenyl-CO-
9e: 7-NO_2-anthracen-1-yl-CO-
9f: (3-phenyl-2-cyanomethoxyphenyl)-CO-
9g: 5-(2-Cl-3-CF_3-phenyl)-furan-2-yl-CO-
9h: 5-(4-Cl-phenyl)-furan-2-yl-CO-
9i: 5-(pyrid-2-yl)-thiophen-2-yl-CO-
9j: (2-CH_3O-phenyl)ethyl-CO-
9k: (3-benzopyrrolyl)ethyl-CO-
9l: (N-phenyl-5-propyl-imidazol-4-yl)-CO-
9m: 1-naphthyl-SO_2-
9n: 5-(isoxazol-2-yl)-thiophen-2-yl-SO_2-

Table 5 (cont.)



Ex#	R^9	A^4	A^3	A^2	R^1	X	Y	Z
100	9a - 9n	Ile	Leu	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
101	9a - 9n	Val	Leu	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
102	9a - 9n	Dpa	Leu	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
103	9a - 9n	Ile	Val	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
104	9a - 9n	Val	Val	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
105	9a - 9n	Dpa	Val	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
106	9a - 9n	Ile	Glu	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
107	9a - 9n	Val	Glu	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
108	9a - 9n	Dpa	Glu	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
109	9a - 9n	Ile	Leu	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
110	9a - 9n	Val	Leu	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
111	9a - 9n	Dpa	Leu	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
112	9a - 9n	Ile	Val	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
113	9a - 9n	Val	Val	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
114	9a - 9n	Dpa	Val	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
115	9a - 9n	Ile	Glu	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
116	9a - 9n	Val	Glu	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
117	9a - 9n	Dpa	Glu	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
118	9a - 9n	Ile	Leu	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
119	9a - 9n	Val	Leu	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
120	9a - 9n	Dpa	Leu	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
121	9a - 9n	Ile	Val	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
122	9a - 9n	Val	Val	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
123	9a - 9n	Dpa	Val	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
124	9a - 9n	Ile	Glu	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
125	9a - 9n	Val	Glu	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
126	9a - 9n	Dpa	Glu	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
127	9a - 9n	bond	Leu	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
128	9a - 9n	bond	Val	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
129	9a - 9n	bond	Glu	Cha	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67

130	9a - 9n	bond	Leu	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
131	9a - 9n	bond	Val	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
132	9a - 9n	bond	Glu	Hyp	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
133	9a - 9n	bond	Leu	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
134	9a - 9n	bond	Val	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
135	9a - 9n	bond	Glu	Pro	1a - 1bw	-(C=O)-	$-SO_2-$	Z1 - Z67
136	9a - 9n	Ile	Leu	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
137	9a - 9n	Val	Leu	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
138	9a - 9n	Dpa	Leu	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
139	9a - 9n	Ile	Val	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
140	9a - 9n	Val	Val	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
141	9a - 9n	Dpa	Val	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
142	9a - 9n	Ile	Glu	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
143	9a - 9n	Val	Glu	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
144	9a - 9n	Dpa	Glu	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
145	9a - 9n	Ile	Leu	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
146	9a - 9n	Val	Leu	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
147	9a - 9n	Dpa	Leu	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
148	9a - 9n	Ile	Val	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
149	9a - 9n	Val	Val	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
150	9a - 9n	Dpa	Val	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
151	9a - 9n	Ile	Glu	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
152	9a - 9n	Val	Glu	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
153	9a - 9n	Dpa	Glu	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
154	9a - 9n	Ile	Leu	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
155	9a - 9n	Val	Leu	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
156	9a - 9n	Dpa	Leu	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
157	9a - 9n	Ile	Val	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
158	9a - 9n	Val	Val	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
159	9a - 9n	Dpa	Val	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
160	9a - 9n	Ile	Glu	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
161	9a - 9n	Val	Glu	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
162	9a - 9n	Dpa	Glu	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
163	9a - 9n	bond	Leu	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
164	9a - 9n	bond	Val	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
165	9a - 9n	bond	Glu	Cha	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
166	9a - 9n	bond	Leu	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
167	9a - 9n	bond	Val	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
168	9a - 9n	bond	Glu	Hyp	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
169	9a - 9n	bond	Leu	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
170	9a - 9n	bond	Val	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
171	9a - 9n	bond	Glu	Pro	1a - 1bw	$-SO_2-$	-(C=O)-	Z1 - Z67
172	9a - 9n	Ile	Leu	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
173	9a - 9n	Val	Leu	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
174	9a - 9n	Dpa	Leu	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
175	9a - 9n	Ile	Val	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
176	9a - 9n	Val	Val	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
177	9a - 9n	Dpa	Val	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
178	9a - 9n	Ile	Glu	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
179	9a - 9n	Val	Glu	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
180	9a - 9n	Dpa	Glu	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
181	9a - 9n	Ile	Leu	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
182	9a - 9n	Val	Leu	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
183	9a - 9n	Dpa	Leu	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
184	9a - 9n	Ile	Val	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
185	9a - 9n	Val	Val	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
186	9a - 9n	Dpa	Val	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
187	9a - 9n	Ile	Glu	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
188	9a - 9n	Val	Glu	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67

189	9a - 9n	Dpa	Glu	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
190	9a - 9n	Ile	Leu	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
191	9a - 9n	Val	Leu	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
192	9a - 9n	Dpa	Leu	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
193	9a - 9n	Ile	Val	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
194	9a - 9n	Val	Val	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
195	9a - 9n	Dpa	Val	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
196	9a - 9n	Ile	Glu	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
197	9a - 9n	Val	Glu	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
198	9a - 9n	Dpa	Glu	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
199	9a - 9n	bond	Leu	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
200	9a - 9n	bond	Val	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
201	9a - 9n	bond	Glu	Cha	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
202	9a - 9n	bond	Leu	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
203	9a - 9n	bond	Val	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
204	9a - 9n	bond	Glu	Hyp	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
205	9a - 9n	bond	Leu	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
206	9a - 9n	bond	Val	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
207	9a - 9n	bond	Glu	Pro	1a - 1bw	-(C=O)-	-(C=O)-	Z1 - Z67
208	9a - 9n	Ile	Leu	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
209	9a - 9n	Val	Leu	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
210	9a - 9n	Dpa	Leu	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
211	9a - 9n	Ile	Val	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
212	9a - 9n	Val	Val	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
213	9a - 9n	Dpa	Val	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
214	9a - 9n	Ile	Glu	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
215	9a - 9n	Val	Glu	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
216	9a - 9n	Dpa	Glu	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
217	9a - 9n	Ile	Leu	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
218	9a - 9n	Val	Leu	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
219	9a - 9n	Dpa	Leu	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
220	9a - 9n	Ile	Val	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
221	9a - 9n	Val	Val	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
222	9a - 9n	Dpa	Val	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
223	9a - 9n	Ile	Glu	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
224	9a - 9n	Val	Glu	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
225	9a - 9n	Dpa	Glu	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
226	9a - 9n	Ile	Leu	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
227	9a - 9n	Val	Leu	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
228	9a - 9n	Dpa	Leu	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
229	9a - 9n	Ile	Val	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
230	9a - 9n	Val	Val	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
231	9a - 9n	Dpa	Val	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
232	9a - 9n	Ile	Glu	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
233	9a - 9n	Val	Glu	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
234	9a - 9n	Dpa	Glu	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
235	9a - 9n	bond	Leu	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
236	9a - 9n	bond	Val	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
237	9a - 9n	bond	Glu	Cha	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
238	9a - 9n	bond	Leu	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
239	9a - 9n	bond	Val	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
240	9a - 9n	bond	Glu	Hyp	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
241	9a - 9n	bond	Leu	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
242	9a - 9n	bond	Val	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67
243	9a - 9n	bond	Glu	Pro	1a - 1bw	$-SO_2-$	$-SO_2-$	Z1 - Z67

UTILITY

The compounds of Formula (I) are expected to inhibit the activity of Hepatitis C Virus NS3 protease. The NS3 protease inhibition is demonstrated using assays for NS3 protease activity, for example, using the assay described below for assaying inhibitors of NS3 protease. The compounds of Formula (I) are expected to show activity against NS3 protease in cells, as demonstrated by the cellular assay described below. Thus, the compounds of Formula (I) are potentially useful in the cure and prevention of HCV infections.

Expression and Purification of NS3 Protease

The plasmid cf1SODp600, containing the complete coding region of HCV NS3 protease, genotype 1a, was obtained from ATCC (database accession: DNA Seq. Acc. M62321, originally deposited by Chiron Corporation). PCR primers were designed that allow amplification of the DNA fragment encoding the NS3 protease catalytic domain (amino acids 1 to 192) as well as its two N-terminal fusions, a 5 amino acid leader sequence MGAQH (serving as a expression tag) and a 15 amino acid His tag MRGSHHHHHHMGAQH. The NS3 protease constructs were cloned in the bacterial expression vector under the control of the T7 promoter and transformed in *E. coli* BL 21 (DE3) cells. Expression of the NS3 protease was obtained by addition of 1 mM IPTG and cells were growing for additional 3h at 25°C. The NS3 protease constructs have several fold difference in expression level, but exhibit the same level of solubility and enzyme specific activity. A typical 10 L fermentation yielded approximately 200 g of wet cell paste. The cell paste was stored at -80°C. The NS3 protease was purified based on published procedures (Steinkuhler C. et al. *Journal of Virology* 70, 6694-6700, 1996 and Steinkuhler C. et al. *Journal of Biological Chemistry* 271, 6367-6373, 1996.) with some modifications. Briefly, the cells were resuspended in lysis buffer (10 mL/g) containing PBS buffer (20 mM sodium phosphate, pH 7.4, 140 mM NaCl), 50%

glycerol, 10 mM DTT, 2% CHAPS and 1mM PMSF. Cell lysis was performed with use of microfluidizer. After homogenizing, DNase was added to a final concentration 70 U/mL and cell lysate was incubated at 4°C for 20 min. After centrifugation at 18,000 rpm for 30 min at 4°C supernatant was applied on SP Sepharose column (Pharmacia), previously equilibrated at a flow rate 3 mL/min in buffer A (PBS buffer, 10% glycerol, 3 mM DTT). The column was extensively washed with buffer A and the protease was eluted by applying 25 column volumes of a linear 0.14 - 1.0 M NaCl gradient. NS3 containing fractions were pooled and concentrated on an Amicon stirred ultrafiltration cell using a YM-10 membrane. The enzyme was further purified on 26/60 Superdex 75 column (Pharmacia), equilibrated in buffer A. The sample was loaded at a flow rate 1 mL/min, the column was then washed with a buffer A at a flow rate 2 mL/min. Finally, the NS3 protease containing fractions were applied on Mono S 10/10 column (Pharmacia) equilibrated in 50 mM Tris.HCl buffer, pH 7.5, 10% glycerol and 1 mM DTT and operating at flow rate 2 mL/min. Enzyme was eluted by applying 20 column volumes of a linear 0.1 - 0.5 M NaCl gradient. Based on SDS-PAGE analysis as well as HPLC analysis and active site titration, the purity of the HCV NS3 1a protease was greater than 95%. The enzyme was stored at -70°C and diluted just prior to use.

Enzyme Assays

Concentrations of protease were determined in the absence of NS4a by using the peptide ester substrate Ac-DED(Edans)EEAbuψ[COO]ASK(Dabcyl)-NH_2 (Taliani et al. *Anal. Biochem.* 240, 60-67, 1996.) and the inhibitor, H-Asp-Glu-Val-Val-Pro-boroAlg-OH and the inhibitor, H-Asp-Glu-Val-Val-Pro-boroAlg-OH and by using tight binding reaction conditions (Bieth, *Methods Enzymol.* 248, 59-85, 1995). Best data was obtained for an enzyme level of 50 nM. Alternately, protease (63 μg/ml) was allowed to react with 3 μM NS4a, 0.10 mM Ac-Glu-Glu-Ala-Cys-*p*NA, and varying

level of H-Asp-Glu-Val-Val-Pro-boroAlg-OH (0-6 μM). Concentrations of protease were determined from linear plots of Activity vs. [inhibitor]. Molar concentrations of proteases were determined from the x-intercept.

K_m values were determined measuring the rate of hydrolysis of the ester substrate over a range of concentrations from 5.0 to 100 μM in the presence of 3 μM KKNS4a (KKGSVVIVGRIVLSGKPAIIPKK). Assay were run at 25°C, by incubating ~1 nM enzyme with NS4a for 5 min in 148 μl of buffer (50 mM Tri buffer, pH 7.0, 50% glycerol, 2% Chaps, and 5.0 mM DTT. Substrate (2.0 μl) in buffer was added and the reaction was allowed to proceed for 15 min. Reactions were quenched by adding 3.0 μL of 10% TFA, and the levels of hydrolysis were determined by HPLC. Aliquots (50 μL) were injected on the HPLC and linear gradients from 90% water, 10% acetonitrile and 0.10 % TFA to 10% water, 90% acetonitrile and 0.10% TFA were run at a flow rate of 1.0 mL/min over a period of 30 min. HPLCs were run on a HP1090 using a Rainin 4.6 x 250 mm C18 column (cat # 83-201-C) fluorescent detection using 350 and 500 nm as excitation and emission wavelengths, respectively. Levels of hydrolysis were determined by measuring the area of the fluorescent peak at 5.3 min. 100% hydrolysis of a 5.0 μM sample gave an area of 7.95 ±0.38 fluorescence units.). Kinetic constants were determined from the iterative fit of the Michaelis equation to the data. Results are consistent with data from Liveweaver Burk fits and data collected for the 12.8 min peak measured at 520 nm.

Enzyme activity was also measured by measuring the increase in fluorescence with time by exciting at 355 nm and measuring emission at 495 nm using a Perkin Elmer LS 50 spectrometer. A substrate level of 5.0 μM was used for all fluorogenic assays run on the spectrometer.

Inhibitor Evaluation *In vitro*

Inhibitor effectiveness was determined by measuring enzyme activity both in the presence and absence of inhibitor. Velocities were fit to the equation for competitive inhibition for individual reactions of inhibitors with the enzyme using

$$v_i / v_o = [K_m (1 + I/K_i) + S] / [K_m + S].$$

The ratio v_i / v_o is equal to the ratio of the Michaelis equations for velocities measured in the presence (v_i) and absence (v_o) of inhibitor. Values of v_i / v_o were measured over a range of inhibitor concentrations with the aid of an Excel™ Spreadsheet. Reported K_i values are the average of 3-5 separate determinations. Under the conditions of this assay, the IC_{50} and K_is are comparable measures of inhibitor effectiveness.

Using the methodology described above, compounds of the present invention were found to exhibit K_i's of $\leq$60 μM, thereby confirming the utility of the compounds of the present invention as effective NS3 protease inhibitors. Preferred compounds of the present invention have K_i's of $\leq$1 μM. More preferred compounds of the present invention have K_i's of $\leq$100 nM. Most preferred compounds of the present invention have K_i's of $\leq$10 nM.

Inhibitor Evaluation in Cell Assay.

The following method was devised to assess inhibitory action of test compounds on the HCV NS3 protease in cultured cells. Because it is not possible to efficiently infect cells with hepatitis C virus, an assay was developed based on co-expression in transfected cell lines of two plasmids, one is able to direct synthesis of the NS3 protease and the other to provide a polypeptide analogous to a part of the HCV non-structural protein containing a single known peptide sequence highly susceptible to cleavage by the protease. When installed in cultured cells by one of a variety of standard methods, the substrate plasmid produces a stable polypeptide of approximately

50KD, but when the plasmid coding for the viral protease is co-expressed, the enzymatic action of the protease hydrolyzes the substrate at a unique sequence between a cysteine and a serine pair, yielding products which can be detected by antibody-based technology, eg, a western blot. Quantitation of the amounts of precursor and products can be done by scanning film auto-radiograms of the blots or direct luminescense-based emissions from the blots in a commercial scanning device. The general organization of the two plasmids is provided in Scheme 6. The coding sequences for the NS3 protease and the substrate were taken from genotype 1a of HCV, but other genotypes, eg 2a, may be substituted with similar results.

The DNA plasmids are introduced into cultured cells using electroporation, liposomes or other means. Synthesis of the protease and the substrate begin shortly after introduction and may be detected within a few hours by immunological means. Therefore, test compounds are added at desired concentrations to the cells within a few minutes after introducing the plasmids. The cells are then placed in a standard CO_2 incubator at 37°C, in tissue culture medium eg Dulbecco-modified MEM containing 10% bovine serum. After 6-48 hours, the cells are collected by physically scraping them from plastic dishes in which they have been growing, centrifuging them and then lysing about 10^6 of the concentrated cells in a minimal volume of buffered detergent, eg 20 µl of 1% sodium dodecyl sulfate in 0.10 M Tris-HC1, pH 6.5, containing 1% mercaptaethanol and 7% glycerol. The samples are then loaded onto a standard SDS polyacrylamide gel, the polypeptides separated by electrophoresis, and the gel contents then electroblotted onto nitrocellulose or other suitable paper support, and the substrate and products detected by decoration with specific antibodies.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various

equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

Preparation of H-Asp-Glu-Val-Val-Pro-boroAlg pinanediol ester•trifluoroacetate

Preparation of Boc-Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-OH.

Boc-Val-Pro-OBzl was prepared by dissolving H-Pro-OBzl (20 g, 83 mmol) in 50 mL of chloroform and adding Boc-Val-OH (18.0 g, 83 mmol), HOBt (23.0g, 165 mmol), NMM (9.0 mL, 83 mmol) and DCC (17.0 g, 83 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was filtered and solvent was evaporated. Ethyl acetate was added and insoluble material was removed by filtration. The filtrate was washed with 0.2N HCl, 5% $NaHCO_3$, and saturated aqueous NaCl. It was dried over Na_2SO_4, filtered and evaporate to give a white solid (30 g, 75 mmol, 90%). ESI/MS calculated for $C_{22}H_{32}N_2O_5$ +H: 405.2. Found 405.6.

Boc-Val-Val-Pro-OBzl was prepared by dissolving Boc-Val-Pro-OBzl (14.0 g, 35.0 mmol) in 4N HCl in dioxane (20 mL) and allowing the reaction to stir for 2h under an inert atmosphere at room temperature. The reaction mixture was concentrated by evaporation *in vacuo* and ether was added to yield a precipitate. It was collected by filtration under nitrogen. After drying *in vacuo* with P_2O_5, H-Val-Pro-OBzl was obtained as a white solid (22.6 g, 30.3 mmol, 89%). (ESI/MS calculated for $C_{17}H_{24}N_2O_3$ +H: 305.2. Found: 305.2.) H-Val-Pro-OBzl (9.2 g, 27 mmol) was dissolved in 50 mL of CH_2Cl_2 and Boc-Val-OH (7.3 g, 27 mmol), HOBt (7.3 g, 54 mmol), NMM (3.0 mL, 27 mmol) and DCC (5.6 g, 27 mmol) were added. The reaction mixture stirred overnight at room temperature. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in ethyl acetate and the solution was re-filtered. The filtrate was washed with

0.2N HCl, 5% $NaHCO_3$, and saturated aqueous NaCl. It was dried over Na_2SO_4, filtered and evaporated to give a yellow oil (10.6 g, 21.1 mmol, 78%). ESI/MS calculated for $C_{27}H_{41}N_3O_6$ + Na: 526.3 Found: 526.4.

Z-Glu(O^tBu)-Val-Val-Pro-OBzl was also prepared by DCC coupling. H-Val-Val-Pro-OBzl•hydrochloride was obtained in a 100% yield by treating the corresponding Boc compound with anhydrous HCl using the procedure described for H-Val-Pro-OBzl (ESI/MS calculated for $C_{22}H_{33}N_3O_4$ + H: 404.2. Found 404.3.). The amine hydrochloride (7.40 g, 16.8 mmol) was dissolved in 185 mL DMF and 25 mL THF. Z-Glu(O^tBu)-OH (5.60 g, 16.8 mmol), HOBt (4.60 g, 33.6 mmol), NMM (1.85 mL, 16.8 mmol) and DCC (3.5 g, 16.8 mmol) were added. The reaction was run and the product was isolated by the procedure described for Boc-Val-Val-Pro-OBzl. The tetrapeptide was obtained as a white foam (12.0 g, 16.1 mmol, 96%). ESI/MS calculated for $C_{39}H_{54}N_4O_9$ + Na: 745.4. Found: 745.4.

H-Glu(O^tBu)-Val-Val-Pro-OH was prepared by dissolving Z-Glu(O^tBu)-Val-Val-Pro-OBzl (2.90 g, 3.89 mmol) in 100 mL methanol containing 1% acetic acid. Pearlman's catalyst, $Pd(OH)_2$, (100mg) was added and the flask was placed on the Parr hydrogenation apparatus with an initial H_2 pressure of 34 psi. After three hours, the catalyst was removed by filtration through a celite pad and the filtrate was evaporated *in vacuo* to yield a yellow oil (1.30 g, 2.61 mmol, 67%). ESI/MS calculated for $C_{24}H_{42}N_4O_7$ +H: 499.3 Found: 499.4.

Boc-Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-OH was prepared by active ester coupling. Boc-Asp(O^tBu)-N-hydroxysuccinimide ester was prepared by coupling Boc-Asp(OtBu)-OH (3.00 g, 10.4 mmol) to N-hydroxysuccinimide (1.19 g, 10.4 mmol) in 50 mL of ethylene glycol dimethyl ether. The reaction flask was placed in an ice bath at 0°C and DCC was added.

The reaction mixture was slowly allowed to warm to room temperature and to stir overnight. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and re-filtered. The filtrate was evaporated give a white solid. Recrystallized from ethyl acetate: hexane gave the activated ester (3.38 g, 8.80 mmol, 84%). (ESI/MS calculated for $C_{17}H_{26}N_2O_8$ + H: 387.2. Found: 387.4.) H-Glu(O^tBu)-Val-Val-Pro-OH (5.40 g, 10.8 mmol) was dissolved in 100 mL of water. Sodium bicarbonate (0.92 g, 11.0 mmol) was added followed by triethylamine (2.30 mL, 16.5 mmol). The N-hydroxysuccinimide ester (3.84 g, 10.0 mmol) was dissolved in 100 mL dioxane and was added to the H-Glu(O^tBu)-Val-Val-Pro-OH solution. The mixture stirred overnight at room temperature. Dioxane was removed *in vacuo* and 1.0 M HCl was added to give pH ~ 1. The product was extracted into ethyl acetate. The ethyl acetate solution was washed with 0.2 N HCl, dried over sodium sulfate, filtered, and evaporated to yield a yellow oil (7.7 g, 10.0 mmol, 100%). ESI/MS calculated for $C_{37}H_{63}N_5O_{12}$ + Na: 792.4. Found: 792.4.

Boc-Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-boroAlg-pinanediol was prepared by coupling the protected pentapeptide to H-boroAlg-pinanediol. Boc-Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-OH (1.8 g, 2.3 mmol) was dissolved 10 mL THF and was cooled to -20°C. Isobutyl chloroformate (0.30 mL, 2.3 mmol) and NMM (0.25 mL, 2.3 mmol) were added. After 5 minutes, this mixture was added to H-boroAlg-pinanediol (0.67 g, 2.3 mmol) dissolved in THF (8 mL) at -20°C. Cold THF (~5 mL) was used to aid in the transfer. Triethylamine (0.32 mL, 2.3 mmol) was added and the reaction mixture was allowed to come to room temperature and to stir overnight. The mixture was filtered and solvent was removed by evaporation. The residue was dissolved in ethyl acetate, washed with 0.2 N HCl, 5% $NaHCO_3$, and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and

evaporated to yield a yellow oil. Half of the crude product (1.5 g) was purified in 250 mg lots by HPLC using a 4 cm x 30 cm Rainin C-18 reverse phase column. A gradient from 60: 40 acetonitrile: water to 100% acetonitrile was run over a period of 28 minutes at a flow rate of 40 mL/min. The fractions containing the desired product were pooled and lyophilized to yield a white solid (46 mg). ^{1}H-NMR (CD_3OD) δ 0.9-1.0 (m, 15H), 1.28 (s, 3H), 1.3 (s,3H), 1.44 (3s, 27H), 1.6-2.8 (20H), 3.7(m,1H), 3.9(m, 1H), 4.1-4.7 (7H), 5.05(m, 2H), 5.9(m, 1H). High res (ESI/MS) calculated for $C_{51}H_{86}N_6O_{13}B_1$ +H: 1001.635. Found 1001.633.

Preparation of H-Asp-Glu-Val-Val-Pro-boroAlg pinanediol ester•trifluoroacetate: The hexapeptide analog, Boc-Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-boroAlg-pinanediol, (22.5 mg, 0.023 mmol) was treated with 2 mL of TFA: CH_2Cl_2 (1: 1) for 2 h. The material was concentrated *in vacuo* and purified by HPLC using C-18 Vydac reverse phase (2.2 x 25 cm) column with a gradient starting at 60:40 acetonitrile/water with 0.1%TFA going to 95:5 over 25 minutes with a flow rate of 8 mL/min. The product eluted at 80% acetonitrile. The fractions were evaporated and dried under high vacuum to give 8.9 mg (49%) of the desired product as white amorphous solid. ^{1}H-NMR (CD_3OD) δ 5.82 (m, 1H), 5.02 (m, 2H), 4.58(m, 1H), 4.42 (m, 3H), 4.18 (m, 4H), 3.90 (m, 1H), 3.62 (m, 1H), 3.01 (dd, 1H), 2.78 (m, 1H), 2.62 (m, 1H), 2.41-1.78 (m, 17H), 1.31 (s, 3H), 1.28 (s, 3H), 1.10 - 0.82 (m, 15H). ESI/MS calculated for $C_{38}H_{62}N_6O_{11}B$ +H: 789.2. Found: 789.2.